Study 1

4-Week Oral Toxicity Study in Rats Followed by a 2-Week Recovery Period, March 4, 2011

[redacted]

[redacted]

4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FINAL REPORT

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4-WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY A 2 WEEK RECOVERY PERIOD

[redacted]

FINAL REPORT

We, the undersigned, were responsible for the preparation of this report.

[redacted] [redacted] Date [redacted]
(Study Director)

[redacted] [redacted] Date [redacted]
(Study Pathologist)

COMPLIANCE STATEMENT

We, the undersigned, hereby declare that the following report constitutes a true and faithful account of the procedures adopted, and the results obtained in the performance of the study. With the exception of the historical control data, that were not revised by Q.A., all other aspects of the study conducted by [redacted] were performed in accordance with:

A. Decreto Legislativo 27 Gennaio 1992 n. 120, *Adoption of 88/320/EEC and 90/18/EEC Directives on the inspection and verification of good laboratory practice (G.U. 18 Febbraio 1992 n. 40)* and subsequent revisions.

B. Directive 2004/10/EC of European Parliament and of the Council of 11 February 2004. *On the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances.*

C. ENV/MC/CHEM(98)17 *OECD principles on Good Laboratory Practice (as revised in 1997).*

[redacted] [redacted] Date [redacted]
(Study Director)

[redacted] [redacted] Date [redacted]
(Scientific Director)

QUALITY ASSURANCE STATEMENT

(Relevant to those aspects of the study conducted by [redacted])

Study phases monitored by [redacted] According to current relevant Standard Operating Procedures	Quality Assurance Inspections (Day Month Year)		
	Inspection	Report to Study Director	Report to Company Management
PROTOCOL CHECK	24.03.2005	24.03.2005	24.03.2005
STUDY-BASED INSPECTIONS RELATED TO THIS TYPE OF STUDY			
Allocation	24.03.2005	29.03.2005	29.03.2005
Dose preparation	01.04.2005	04.04.2005	04.04.2004
Dosing (oral)	31.03.2005	20.04.2005	22.04.2005
Pre post dose observation	31.03.2005	22.04.2005	22.04.2005
Body weight	07.04.2005	01.06.2005	09.06.2005
Food consumption	21.04.2005	22.04.2005	22.04.2005
Clinical observations	05.04.2005	07.04.2005	07.04.2005
Functional observation battery	05.04.2005	07.04.2005	07.04.2005
Sensory reactivity to stimuli	22.04.2005	13.05.2005	13.05.2005
Blood sampling	28.04.2005	01.06.2005	09.06.2005
Urine collection	28.04.2005	29.04.2005	29.04.2005
Timed bleed	15.04.2005	22.04.2005	22.04.2005
Necropsy	28.04.2005	01.06.2005	09.06.2005

QA inspection regarding Analytical Chemistry, Histology and Clinical Pathology Departments as well as regarding other routine activity not directly related to this study are carried out as process-based inspections. The relevant documentation is kept on file although specific inspection dates are not reported here.

Associated laboratories and support functions are subject to regular facility inspections.

FINAL REPORT	Review completed
Review of this report by [redacted] found the reported methods and procedures to describe those used and the results to constitute an accurate representation of the recorded raw data. Addendum VII Historical control data was not verified by QAU.	17 Oct 2006

[redacted]

17 Oct 2006

Date

[redacted]

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Addenda

1. SUMMARY

1.1 The oral toxicity of [redacted] when given by daily administration to rats, has been investigated over a period of 4 consecutive weeks and recovery from any potential treatment-related effects over a period of 2 consecutive weeks.
Three groups, each of 5 male and 5 female Sprague Dawley rats, received the test item by gavage at dosages of 0.3, 0.8 and 2.0 mg/kg/day for 4 consecutive weeks. A fourth similarly constituted group received the vehicle alone (distilled water) and acted as a control. Five additional animals for each sex were included in the high and control groups for recovery assessment. Blood samples were also taken following a single dose from a satellite group of 9 males and 9 females, dosed at 2.0 mg/kg/day, for toxicokinetic evaluations.

1.2 Mortality

One female animal dosed at 0.3 mg/kg/day was found dead on Day 23 of treatment. This death was not considered treatment-related.

1.3 Pre- and post-dose observations and weekly clinical signs

No signs were observed at daily post-dose observations.
Detailed clinical signs with neurotoxicity assessment did generally not show any signs which could be correlated to the treatment with the test item.

1.4 Motor activity and sensory reaction to stimuli

A dose–related reduction of grip strength was observed in the treated males and in the mid- and high dose females at the end of treatment when compared to controls. No significant differences were observed at evaluations performed at the end of recovery.
Motor activity measurements performed at the end of treatment and recovery periods did not show changes which could be ascribed to treatment.

1.5 Body weight

Body weights showed statistically significant reductions in the high dose animals from Day 22 up to the end of the treatment period when compared to controls. Terminal body weight was also significantly reduced in the high dose animals. These reductions were still evident up to the end of the recovery period.

1.6 Food consumption

A reduction of food intake was observed at the end of the treatment phase in the high dose males. Food intake was still significantly reduced at the end of the first week of recovery and, in the males, also at the end of the recovery period.

1.7 Haematology

A decrease in white blood cells (lymphocytes in both sexes, neutrophils in the males) was observed in the high dose animals and in the mid-dose females. In addition, the prothrombin time was slightly increased in the high dose males. These changes showed a trend for recovery after the treatment-free period.
No other alterations in the haematological parameters were observed.

1.8 Clinical chemistry

Dose related changes observed at the clinical chemistry investigations performed during week 4 of treatment revealed alteration of liver function in the high dose males and, to a lesser extent, in two mid-dose males (increases in hepatic markers alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and total bilirubin, decrements in protein, globulin and albumin). A reversibility of these changes was observed for the aminotransferase enzymes. No significant hepatic marker alterations were observed in females.

Urea plasma levels were increased in high dose animals, while creatinine and inorganic phosphorus showed a decrement in the same group.
At the end of the recovery period, no complete reversibility of such changes was observed.
No other changes of biological significance were observed.

1.9 Urinalysis

No alterations in urine were observed which could be attributed to treatment.

1.10 Toxicokinetic analysis

Detectable plasma levels of the test item were measured between 2 and 216 hours after dosing in the animals dosed at 2.0 mg/kg. Maximum plasma levels (C_{max}), calculated separately for each of the [redacted] were within the range of 124.3 – 4545.4 ng/ml in the males and 160.7 – 4581.3 ng/ml in the females. In both cases, [redacted] showed the highest concentration.
C_{max} was generally measured 24 hours after dosing (t_{max}). Athough in some fractions measured in the females different t_{max} were obtained. The estimated half-life ($t_{½}$) was comprised in the range of 201 - 544 hours for males and 39 - 2185 hours for females. The AUC was calculated to be from 22516 to 791984 ng/ml·h in the males and 26563 to 584697 ng/ml·h in the females.
$AUC_{(inf)}$ was calculated to be in the ranges of 57915 - 3249932 and 44431 - 877949 ng/ml·h in males and females, respectively.

1.11 Organ weights

Dose-related, statistically significant increases in absolute and relative liver weights were noted in all treated males and in mid- and high dose females at the end of the treatment period. This increase was still present at the end of recovery. In addition, statistically significant reductions of the absolute and relative weights of the spleen and thymus and increases of the relative weights of the thyroid, kidneys, epididymides and testes were seen in the high dose animals at the end of treatment. All these organs (spleen, kidneys, epididymides, testes, thyroid and thymus) still showed differences from controls at the end of recovery.

1.12 Macroscopic observations

The most relevant changes, observed at necropsy of the early decedent animal, were dark red contents in the abdominal cavity and 2 dark, ruptured areas in the liver.
Pale colour of the liver, sometimes accompanied by swollen shape of the organ, was reported in mid- and high dose males and 1 high dose female. Decreased size of the thymus and transparent seminal vesicles were also seen in high dose males.
Enlargement of the liver and renal pelvis dilatation was recorded in 2/5 treated males at the end of the recovery phase.

1.13 Microscopic observations

Multifocal, mild haemorrhages were reported in the liver of the early decedent animal. This finding, along with the macroscopic observation in the abdominal cavity, suggests that this death could be considered spontaneous or accidental in origin.

Liver: hepatocytic hypertrophy was observed in all high dose group animals, all mid-dose males and 4/5 low dose males. This finding showed mainly a panlobular distribution in the high dose group males, while it was limited to the centrilobular, mid-zonal areas in the remaining main phase animals.
Lungs: aggregation of alveolar macrophages was seen in the lungs of 4/5 males and 2/5 females from the high dose group.
Thymus: slight to moderate atrophy was observed in 3/5 males and in 1 female from the high dose group.

Only a partial remission of the changes considered related to the administration of the test item was observed following the 2-week recovery period.
Liver: hepatocytic hypertrophy was still evident in all treated animals.
Lungs: instances of focal aggregation of alveolar macrophages were seen in the lungs of 1 treated male and 1 treated female.
Thymus: moderate atrophy was observed in 1 treated male.

Colloid depletion was observed in the seminal vesicles of 3/5 high dose group males. Hepatocytic necrosis was observed in 2/5 high dose and 1/5 intermediate dose males in the main phase and in 1 treated male from the recovery group. The above changes, as well as the moderate chronic inflammation reported in the liver of 1 high dose male killed at termination of the treatment phase, were considered to be unspecific, possibly linked to the general condition of the treated animals and spontaneous in origin.

The remaining findings reported in the animals sacrificed after completion of the scheduled test periods and in the unscheduled dead animal were considered to be incidental or spontaneous in origin.

1.14 Conclusions

On the basis of the above results, signs of an evident toxic effect of the test item were seen at the 2 higher dose levels (0.8 and 2.0 mg/kg/day). Most of the observed effects were not reversible over a 2 week recovery period in the high dose animals. The findings in the liver, observed at all the doses were a clear indication of a toxic effect of the test item to this organ. Males were clearly more sensitive than females. Also the toxicokinetic half-life values were higher in males than females.
Effects on the main target organ, the liver, although at a lower incidence when compared to those observed at the higher dose levels, were also observed in the males of the low dose level (0.3 mg/kg/day). Besides changes in the liver, only minor effects were observed at 0.3 mg/kg/day in the males. The majority of these effects were not considered adverse, as they were slight, often not dose-related and within the normal range of historical control data. The hepatocytic hypertrophy could be suggestive of an adaptive change. However, the lack of recovery over a 2 week treatment-free period, seen in the high-dose animals, may be an indication of other changes occurring in the liver, not detectable through the standard microscopic examination. Therefore, none of the dose levels investigated may be considered either a No Observed Effect Level (NOEL) or a No Observed Adverse Effect Level (NOAEL) in this study for males. On the contrary, females appeared to be less sensitive than males. At 0.3 mg/kg/day no adverse effects were observed. Therefore this dose can be considered a No Observed Adverse Effect Level (NOAEL) for the females.

2. INTRODUCTION

The purpose of this study was to evaluate the toxicity of [redacted], when administered daily to rats by the oral route for 4 consecutive weeks, and to investigate possible recovery from any treatment-related effects, during a 2 week recovery period.

The study design was in agreement with the procedures described in OECD Guideline No. 407 adopted on 27 July 1995 and with those described by Japanese METI (Ministry of Economy, Trade and Industry), of 13 July 1974 and subsequent revisions.

The Sprague Dawley rat was chosen because it is accepted by many regulatory authorities and there is ample experience and background data on this species and strain.

The oral route was selected as it is a possible route of exposure of the test item in man. The dose levels of 0.3, 0.8 and 2.0 mg/kg/day were defined in agreement with the Sponsor based on information from preliminary studies.

Each main group comprised 5 male and 5 female rats. Control and high dose groups included 5 additional animals per sex that were killed after 2 weeks of recovery. One satellite group for toxicokinetics comprised 9 male and 9 female animals.
No treatment was given during the recovery period.

The animals were assigned to treatment groups on 24 March 2005 and dosing began on 31 March 2005. Necropsies of main groups were completed by 29 April 2005 and recovery groups by 12 May 2005.
The protocol is presented in Addendum VI.

The study was carried out at:

[redacted]

The study was conducted on behalf of:

[redacted]

3. TEST ITEM

Information received from the Sponsor indicated the following:

Name	: [redacted]
Alternative name	: [redacted]
Batch Number of the precursor acid	: 32230N
Batch Number	: 90409/86-I
CAS Number	: [redacted]
Purity	: [redacted]
Expiry date	: 1st January 2015
Received from	: [redacted]
Date received	: 14th January 2005
Amount received	: Approximately 300 grams
Description	[redacted]
Container	: Colourless glass bottle
Storage at [redacted]	: Ambient conditions
[redacted]eference number	: 9372

The determination of the identity, strength, purity, composition and stability of the test item was the responsibility of the Sponsor.
A sample of the test item was taken before commencement of treatment and will be stored in the archives at [redacted] for 10 years prior to disposal.

The test item was dissolved in distilled water to give the required concentrations of 0.03, 0.08 and 0.2 mg/ml.

Prior to commencement of treatment the proposed formulation procedure was checked by chemical analysis to confirm that the method was acceptable. Stability was found to be equivalent to 6 days at room temperature following analysis. Samples of the formulations prepared in weeks 1 and 4 were analysed to check the concentration. Results of all the analyses were within the limits of acceptance (95-105%). Results of these analyses, carried out by the Analytical Chemistry Department a[redacted] are presented in Addendum III of this report.

4. METHODS

4.1 Test system

4.1.1 Animal supply and acclimatisation

A total of 90 Hsd Sprague Dawley rats (45 males and 45 females), 27-29 days old and within a weight range of approximately 75-99 g, were obtained from [redacted]. Animals were delivered in the weight range of 84-101 g, therefore slightly outside the range indicated in the protocol.
After arrival, on 11 March 2005, the weight range for each sex was determined and the animals were temporarily identified within the cage by means of a coloured mark on the tail. A health check was then performed by a veterinarian.
An acclimatisation period of approximately 2 weeks was allowed before the start of treatment, during which time the health status of the rats was assessed by thorough observations.

4.1.2 Animal husbandry

The animals were housed in a limited access rodent facility. Animal room controls were set to maintain temperature and relative humidity at 22°C ± 2°C and 55% ± 15% respectively; actual conditions were monitored, recorded and the records retained. There were approximately 15 to 20 air changes per hour and the rooms were lit by artificial light for 12 hours each day.
The animals were housed up to 5 of one sex to a cage, in clear polycarbonate cages measuring 59x38.5x20 cm with a stainless steel mesh lid and floor ([redacted]). Each cage tray held absorbent paper which was inspected and changed at least 3 times a week.
Drinking water was supplied *ad libitum* to each cage via water bottles, except as noted in section 4.4.
A commercially available laboratory rodent diet ([redacted]) was offered *ad libitum* throughout the study, except as noted in section 4.4.
There was no information available to indicate that any non-nutrient substance likely to influence the effect of the test item was present in the drinking water or the diet. Records of analyses of water and diet are kept on file at [redacted].
Dated and signed records of activities relating to the day to day running and maintenance of the study in the animal house were recorded in a Study Day Book.

4.1.3 Allocation to groups

On the day of allocation (7 days prior to the start of treatment) all animals were weighed. Animals at the extremes of the weight distribution and/or any animal showing signs of ill health were excluded to leave the required number of animals. The rats were allocated to the 5 groups by computerised stratified randomisation to give approximately equal initial group mean body weights.
Individuals were uniquely identified within the study by sex, tattoo on the hind feet, and ear notch and housed up to 5 of one sex per cage.
The cages were identified by a label and recording the study number, animal numbers and details of treatment.
The arrangement of cages in batteries was such that cages from each main group were evenly distributed across the battery (Figure 1) to minimise possible environmental effects.

4.2 Treatment

4.2.1 Selection of dose levels

Dose levels were selected in consultation with the Sponsor based on information from preliminary studies.

4.2.2 Dose levels, group size and identification

Each main group comprised 5 male and 5 female rats. Control and high dose groups included 5 additional animals per sex to be sacrificed after 2 weeks of recovery. One satellite group for toxicokinetics comprised 9 male and 9 female animals. The group identification and animal numbers assigned to the treatment are summarised below:

MAIN GROUPS

Group Number:	Treatment (mg/kg/day)+	Level	Main phase		Rat numbers Recovery phase	
			M (even)	F (odd)	M (even)	F (odd)
1	0.0	Control	2 - 10	1 - 9	12 - 20	11 - 19
2	0.3	Low	22 - 30	21 - 29		
3	0.8	Medium	32 - 40	31 - 39		
4	2.0	High	42 - 50	41 - 49	52 - 60	51 - 59
+: in terms of test item as supplied						

SATELLITE GROUP

Group Number:	Treatment (mg/kg)+	Level	Rat numbers Males (even)	Females (odd)
5	2.0	High	62 - 78	61 - 77
+: in terms of test item as supplied				

The rat numbers listed above formed the last digits of a computer generated 8 figure animal number (the remaining digits of the animal number were different for each concurrent study and served to ensure unique animal numbering for any study employing computerised data collection). The computerised system used in this study was the Xybion Path/Tox System, version 4.2.2.

4.2.3 Administration of test item

The test item was administered orally, by gavage, at a dose volume of 10 ml/kg body weight. Control animals received the vehicle alone at the same dose volume.
The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal.

4.2.4 Duration of treatment

All main group animals were dosed once a day, 7 days a week, for a minimum of 4 consecutive weeks followed by a recovery period of 2 weeks for 5 males and 5 females from groups 1 and 4. Satellite group animals were dosed once only.
All animals from the main groups were dosed up until the day before necropsy.
No treatment was given during the recovery period.

4.3 *In vivo* observations

4.3.1 Mortality

Throughout the study, all animals were checked each working day, early in the morning and in the afternoon. At weekends and Public Holidays a similar procedure was followed except that the final check was carried out at approximately mid-day. This allowed *post mortem* examinations to be carried out during the working period of that day.
A complete necropsy was performed as detailed in section 4.6.2 below.

4.3.2 Pre- and post-dose observations (Main groups)

All observations were recorded for individual animals. Examination of individual animals for signs of reaction to treatment was carried out daily before dosing, immediately after, and approximately 1 and 2 hours after dosing up to Day 10 of the study. Since no animals showed any post-dose effects, examinations were reduced to pre-dose, immediately after and approximately 1 hour after dosing until the end of treatment. These data, as no signs were observed, are not presented in a tabulated form in this report.

4.3.3 Clinical signs and neurotoxicity assessment (Main groups)

All clinical signs were recorded for individual animals. Once before commencement of treatment and once a week thereafter each animal was subjected to a detailed clinical examination, which included an evaluation of neurotoxicity. Animals were examined in an open arena for a period of three minutes. Observed parameters, described by an evaluation scale, are indicated below:

Removal (from cage):	Easy, Difficult, Very difficult
Handling reactivity:	Normal, Slow, Moderate, Marked
Lachrymation:	Absent, Slight, Marked
Palpebral closure:	Absent, Slight, Moderate, Marked
Salivation:	Absent, Slight, Marked
Piloerection:	Absent, Present
Rearing:	Absent, Intervals of number of times (i.e. 1-3, 4-7, 8-10)
Spasms:	Absent, Tonic spasms, Clonic spasms, Tonic-clonic spasms
Myoclonia:	Absent, Present
Mobility impairment:	Absent, Slight, Moderate, Marked
Arousal (animal activity):	Very slow, Slow, Normal, Moderate, Marked
Vocalisation:	Absent, Present
Stereotypies:	Absent, Present
Unusual respiratory pattern:	Absent, Present
Bizarre behaviour:	Absent, Present
Urination:	Absent, Intervals of number of times (i.e. 1-3, 4-6)
Defecation:	Absent, Intervals of number of times (i.e. 1-3, 4-6)
Tremors:	Absent, Present

Gait (one of the following options):	Normal Ataxia (Slight, Moderate, Marked) Hunched (Slight, Moderate, Severely) Pronation Fore limbs drag (Slight, Moderate, Marked) Hind limbs drag (Slight, Moderate, Marked)

All observed parameters, with the exception of the pre-dose, are reported in a group incidence table. Individual data are not included in this report.
Once during week 4 of treatment and once during week 2 of recovery, an evaluation of sensory reactivity to stimuli of different modalities (e.g. auditory, visual and proprioceptive stimuli) and assessment of grip strength were also performed.

4.3.4 Motor activity assessment (MA) (Main groups)

The motor activity of all animals was measured once during week 4 of treatment and week 2 of recovery by an automated activity recording device. Measurements were performed using a computer generated random order.

4.3.5 Body weight

All animals were weighed on the day of allocation to treatment groups, on the day that treatment commenced, weekly thereafter and just prior to necropsy. Satellite group animals were weighed on allocation and on the day of dosing only (data are not included in the report).

4.3.6 Food consumption (Main groups)

The weight of food consumed by each cage of rats was recorded weekly following allocation and the group mean daily intake per rat calculated.

4.4 Clinical pathology investigations (Main groups)

At the end of the 4 week treatment period and again at the end of week 2 of the recovery period, individual overnight urine samples were collected from all surviving animals of the main phase groups under conditions of food and water deprivation. Before starting urine collection, water bottles were removed from each cage and each animal received approximately 10 ml/kg of drinking water by gavage, in order to obtain urine samples suitable for analysis.
On the same days, samples of blood were withdrawn, prior to necropsy, under isofluorane anaesthesia from the abdominal vena cava from the same animals in the same conditions.
Blood samples were collected and analysed in the same order, a computer-generated random cage order being used.

The blood samples collected were divided into tubes as follows:

EDTA anticoagulant	for haematological investigations
Heparin anticoagulant	for biochemical tests
Citrate anticoagulant	for coagulation tests

The measurements performed on blood and urine samples are listed below:

4.4.1 Haematology

Haematocrit
Haemoglobin
Red blood cell count
Reticulocyte count (not performed as no signs of anaemia were evident)
Mean red blood cell volume
Mean corpuscular haemoglobin
Mean corpuscular haemoglobin concentration
White blood cell count
Differential leucocyte count
- Neutrophils
- Lymphocytes
- Eosinophils
- Basophils
- Monocytes
- Large unstained cells

Abnormalities of the blood film
Platelets
Prothrombin time

4.4.2 Clinical chemistry

Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Gamma -glutamyltransferase
Urea
Creatinine
Glucose
Triglycerides
Phosphorus
Total bilirubin
Total cholesterol
Total protein
Albumin
Globulin
A/G Ratio
Sodium
Potassium
Calcium
Chloride

4.4.3 Urinalysis

Appearance
Volume
Specific gravity
PH
Protein
Total reducing substances
Glucose
Ketones
Bilirubin

Urobilinogen
Blood

The sediment, obtained from centrifugation at approximately 3000 rpm for 10 minutes, was examined microscopically for:

Epithelial cells
Poly morphonuclear leucocytes
Erythrocytes
Crystals
Spermatozoa and precursors
Other abnormal components

4.5 Toxicokinetics (Satellite group)

Blood samples were collected at 9 time points from the day of dosing, from all animals of the satellite group as indicated in the following scheme:

Group Number:	Treatment (mg/kg)	Animal Number (Males)	Animal Number (Females)	Time points (hours)
5	2.0	62, 64, 66 68, 70, 72 74, 76, 78	61, 63, 65 67, 69, 71 73, 75, 77	0, 4, 24 2, 8, 168 6, 48, 216

At each sampling time approximately 0.8 ml blood samples were collected from the tail vein of each animal as indicated above. Samples were transferred into tubes containing heparin anticoagulant, centrifuged and the plasma frozen at -20°C. Analysis of the samples was carried out by the Analytical Chemistry Department of [redacted]
Satellite group animals were dosed once only and no necropsy was performed on animals dying during the study or sacrificed at the end of the study. Surviving satellite group animals were killed at the end of the last bleeding procedure. No necropsy examination was performed on these animals.
Analysis of the samples was carried out by the Analytical Chemistry Department of [redacted]
Satellite group animals were dosed once only. Satellite group animals were killed at the end of the last bleeding procedure and no necropsy was performed in these animals.

For each fraction of the test product, the following parameters were calculated according to standard non-compartmental analysis:

C_{max} : maximum observed plasma concentration
T_{max} : time to C_{max}
t½ : half life
AUC and AUC inf : area under the concentration-time curve calculated by the linear trapezoidal rule

Means, standard deviations and kinetic parameters were obtained using a suitable Microsoft Excel Worksheet. Values identified in the tables as BLQ were considered as zero in the calculation of mean and standard deviation for plasma levels.

4.6 Terminal studies

4.6.1 Euthanasia

Animals that had completed the scheduled test period were killed by exsanguination under isofluorane anaesthesia. All animals of the main groups, including that found dead, were subjected to necropsy, supervised by a pathologist, as detailed below. Satellite group animals were killed with carbon dioxide.

4.6.2 Necropsy (Main groups)

The clinical history of the animal was studied and a detailed *post mortem* examination was conducted (including examination of the external surface and orifices).
Changes were noted, the requisite organs weighed and the required tissue samples preserved in fixative and processed for histopathological examination (see sections 4.6.3 to 4.6.5).

4.6.3 Organ weights (Main groups)

From all animals completing the scheduled test period, the organs indicated in section 4.6.6 were dissected free of fat and weighed.
The ratios of organ weight to body weight were calculated for each animal.

4.6.4 Tissues fixed and preserved (Main groups)

Samples of all the tissues listed in section 4.6.6 were fixed and preserved in 10% buffered formol saline (except eyes which were fixed in Davidson's fluid; and testes and epididymides which were fixed in Bouin's solution and all preserved in 70% ethyl alcohol).

4.6.5 Histopathological examination

Tissues listed in section 4.6.6 were fixed and preserved. After dehydration and embedding in paraffin wax, sections of the tissues were cut at 5 micrometre thickness and stained with haematoxylin and eosin. In the first instance, the examination was carried out as detailed below:

a) Tissues specified in section 4.6.6 from all animals in the control and high dose groups of the main phase.
b) Tissues specified in Annex 1 from all animals killed or dying during treatment period.
c) Tissue abnormalities from all main groups (this was a deviation from the protocol which indicated examination of abnormalities from all animals).

On the basis of the results obtained, in agreement with the Sponsor, the examination was extended to the liver, lungs and thymus of low and mid-dose group animals and to the animals which underwent 2 weeks of recovery.

4.6.6 Annex 1 of study protocol

Organs / Tissues	Weight	Fixation Preservation	Microscopic Examination
Abnormalities		✓	✓
Adrenal glands	✓	✓	✓
Bone marrow (from sternum)		✓	✓
Brain	✓	✓	✓
Caecum		✓	✓
Colon		✓	✓
Duodenum		✓	✓
Epididymides	✓	✓	✓
Eyes		✓	*
Heart	✓	✓	✓
Ileum (including Peyer's patches)		✓	✓
Jejunum		✓	✓
Kidneys	✓	✓	✓
Liver	✓	✓	✓
Lungs (including mainstem bronchi)		✓	✓
Lymph nodes - cervical		✓	✓
Lymph nodes - mesenteric		✓	✓
Ovaries	✓	✓	✓
Oviducts[a]		✓	✓
Parathyroid glands[b]		✓	✓
Pituitary gland		✓	✓
Prostate gland		✓	✓
Rectum		✓	✓
Sciatic nerve		✓	✓
Seminal vesicles		✓	✓
Spinal column		✓	*
Spinal cord		✓	✓
Spleen	✓	✓	✓
Stomach		✓	✓
Testes	✓	✓	✓
Thymus (where present)	✓	✓	✓
Thyroid	✓	✓	✓
Trachea		✓	✓
Urinary bladder		✓	✓
Uterus - cervix		✓	✓

*: not examined as no signs of toxicity were observed
a: weighed and preserved with ovaries
b: weighed and preserved with thyroid gland

4.7 Statistical analysis

For continuous variables the significance of the differences amongst groups was assessed by analysis of variance. Differences between each treated group and the control group were assessed by Dunnett's test using a pooled error variance. The homogeneity of the data was verified by Bartlett's test before Dunnett's test. If data were found to be inhomogeneous a Modified t test (Cochran and Cox) was applied. The mean values, standard deviations and statistical analysis were calculated from the actual values in the computer without rounding off.

4.8 Deviations from protocol

Any deviations from protocol are indicated within the text of the report. No deviations occurred which were considered to have compromised the purpose or integrity of the study.

4.9 Archives

Full records were maintained of all aspects of study conduct, together with the results of all measurements and observations.
All specimens, raw data, records and documentation generated during the course of this study will be retained within the archive at [redacted] The data will be kept for a period of 3 years after which the Sponsor will be contacted for instructions regarding despatch or disposal of the material.
Biological samples will be destroyed shortly after the issue of the Final Report.

5. RESULTS

5.1 Mortality (Appendix 1)

One female animal dosed at 0.3 mg/kg/day was found dead on Day 23 of treatment. No clinical signs were seen during the study in this animal. On the basis of the *post mortem* findings, (dark red contents seen in the abdominal cavity and 2 dark, ruptured areas in the liver observed at macroscopic examination along with the multifocal, mild haemorrhage in the liver, seen at microscopic examination). These findings indicate that this death was not treatment-related.

5.2 Pre- and post-dose observations and weekly clinical signs (Open field measurements) (Table 1)

No signs were observed at daily post-dose observations. These data were not tabulated. Detailed clinical signs with neurotoxicity assessment did generally not show any signs which could be correlated to the treatment with the test item.

5.3 Sensory reaction to stimuli and motor activity (Table 2; Appendices 2 and 3)

A dose-related reduction of grip strength was observed in the treated males at the end of treatment when compared to controls (reductions of 35%, 57% and 60%, groups 2, 3, 4 respectively). This parameter was also slightly reduced in the mid- and high dose females (27% and 26% respectively). No significant differences were observed at evaluations performed at the end of recovery.
Motor activity measurements performed at the end of treatment and recovery periods did not show changes which could be ascribed to treatment.

5.4 Body weight (Figure 2; Tables 3, 4 and 7; Appendices 4 and 5)

Body weights showed statistically significant reductions in the high dose animals from Day 22 (7% less than controls in the males) up to the end of the treatment period, when reductions of 21% (main group animals) and 16% (recovery animals) were noted in the males and 9% (main group animals) and 10% (recovery animals) in the females when compared to controls. The slight body weight losses observed in the treated animals may be ascribed to the overnight fast prior to bleeding procedures for clinical pathology analyses. This was not observed in the controls, which showed only a reduced body weight gain. Terminal body weight was also statistically significantly reduced in the high dose animals (20% in the males and 11% in the females). These decreased body weights, due to a reduction of body weight gain, were still evident at the end of the recovery period (25% in the males and 9% in the females). Decreases of body weight gain were correlated to the reduced food intake, observed in the high dose males.

5.5 Food consumption (Appendix 6)

A reduction (20% less than controls) of food intake was observed at the end of the treatment phase in the high dose males. Food intake was still significantly reduced (33%) at the end of the first week of recovery. Slight reductions (9%) were still present in the males at the end of the recovery period.

5.6 Haematology (Table 5; Appendix 7)

A decrease in white blood cell was observed in the high dose animals (approximately 19%) and in the mid-dose females (approximately 17%) at the end of the treatment period. This reduction was still evident at the end of the recovery period (11% and 16% in females and males respectively). The decrement comprised both the lymphocytes and the neutrophils in the males, which had 29%, 19% and 39% less neutrophils at the high, medium and low dose, respectively. Such an evident decrement was not observed in the females.
In addition, the prothrombin time was slightly increased in high dose males (14%). This could reflect the alteration in hepatic functions as indicated by the clinical chemistry results. This change showed a trend for recovery at the end of treatment-free period, when an increase of 8% was observed.

The other differences observed in the haematological parameters (RBC, HGB, HCT, MCHC) were considered to be incidental and of no toxicological significance, since they were observed only during the recovery phase and no other alterations in the same haematological parameters were observed during the treatment period.

5.7 Clinical chemistry (Table 6; Appendix 8)

The statistically significant changes in clinical chemistry parameters are summarized below:

Parameters	2M	3M	4M	4M Rec	2F	3F	4F	4F Rec
AP		+18%	+33%	+41%				
ALT		+309%	+219%					
AST		+58%	+61%					-29%
BILT			+70%			-60%	-33%	-37%
CHOL	-34%	-23%		+76%				
GLU							+20%	+31%
TRI		-51%		-45%				-27%
Urea			+48%	+35%			+24%	
Crea				-34%			-15%	-35%
Prot	-9%		-16%	-11%				
Alb			-13%					+9%
Glo	-14%	-11%	-23%	-26%				
A/G Ratio							+17%	+20%
Cl			+2%				+2%	-1%
Phos		-9%	-21%				-9%	-7%
Na		+4%		-2%				-2%
K								+12%

Changes observed at the clinical chemistry investigations performed during week 4 of treatment revealed an alteration of liver function in the high dose males and, to a lesser extent, in two mid-dose males (increases in hepatic markers alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and total bilirubin, decrements in protein, globulin and albumin). These changes were generally dose related (from approximately 20% to approximately 3 fold) and, in some high dose animals, values were outside the range of historical data.
The above mentioned changes could reflect an alteration in the hepatic function.
A reversibility of these changes was observed for the aminotransferase enzymes at the clinical pathology performed during week 2 of recovery.
No significant hepatic marker alterations were observed in females.

Urea plasma levels were increased in high dose animals, while creatinine and inorganic phosphorus showed a decrement in the same group. At the end of the recovery period, no complete reversibility of such changes was observed. The cause of these changes however remains unclear and could not be conclusively attributed to the test item.
In addition, changes of chloride and sodium serum levels were insufficient in magnitude to be of biological significance.

The other alterations observed during the recovery period in both sexes were considered to be incidental and of no toxicological significance.

5.8 Urinalysis (Table 7; Appendix 9)

No alterations in urine were observed which could be attributed to treatment.

5.9 Toxicokinetic analysis (Figure 3; Addendum IV)

Detectable plasma levels of the test item were measured between 2 and 216 hours after dosing in the animals dosed at 2.0 mg/kg. Maximum plasma levels (C_{max}), calculated separately for each of the [redacted] were as follows: 370.2 and 472.5 ng/ml of [redacted], 124.3 and 160.7 ng/ml of [redacted], 4545.4 and 4581.3 ng/ml of [redacted], 689.3 and 773.8 ng/ml of [redacted] 196.9 and 234.7 ng/ml of [redacted] in the males and females, respectively). C_{max} was generally measured 24 hours after dosing (t_{max}). A t_{max} of 6 hours was observed in the males for [redacted] a t_{max} of 2 hours was observed in the females for [redacted], a t_{max} of 168 hours was observed in the females for [redacted].
The estimated half-life (t½) calculated separately for each [redacted] showed the following figures: 544 and 2185 hours for [redacted], 385 and 346 hours for [redacted], 481 and 39 hours for [redacted], 454 and 763 hours for [redacted], 201 and 160 hours for [redacted] in males and females, respectively. Very high test item plasma levels of all fractions were still present seven days after dosing, particularly in the males.
The AUC was calculated to be 65550 and 77653 ng/ml·h for [redacted], 22516 and 26563 ng/ml·h for [redacted], 791984 and 167950 ng/ml·h for [redacted] 123729 and 130769 ng/ml·h for [redacted], 30768 and 27116 ng/ml·h for [redacted] in the males and females, respectively.
Calculations were generally made from t_{max}, with some exceptions ([redacted] in the females), in which the 24 and 48 hour samples were included in the calculation.
$AUC_{(inf)}$ was calculated to be 299662 and 877949 ng/ml·h for [redacted], 72388 and 63751 ng/ml·h for [redacted], 3249932 and 176042 ng/ml·h for [redacted], 464508 and 584697 ng/ml·h for [redacted], 57915 and 44431 ng/ml·h for [redacted] in males and females, respectively.
Half-life values were obtained by an extrapolation, as no decrements of test item fraction plasma levels were observed at 216 hours post-dose. This situation did not allow the calculation of significant values of the AUC.

5.10 Organ weights (Tables 9 and 10; Appendices 10 and 11)

Dose-related, statistically significant increases in liver weights were noted in all treated males (54% and 84% in mid- and high dose groups for absolute weights, 17%, 57% and 130% greater than controls for relative weights) and in the mid- and high dose females (46% in high dose group for absolute weights, 16% and 65% in mid- and high dose groups for relative weights) at the end of the treatment period. These increases were still present at the end of the recovery period (in the males 89% and 152% and in the females 56% and 71% absolute and relative respectively).
Statistically significant reductions of the absolute (38% in the high dose males, 23% and 36% in the mid- and high dose females) and relative (23% in the high dose males, 20% and 28% in the mid- and high dose females) weights of the spleen were also observed at termination of the treatment period.

In addition the absolute and/or relative weights of the thymus were reduced in high dose males (absolute showing a reduction of 41% and relative of 27%) and the relative weights of the kidneys, epididymides and testes were slightly increased in the high dose males at the end of treatment. An increase of the relative weight of the thyroid (26% and 15% in males and females respectively), statistically significant only in the males, was observed in the high dose animals.
All these organs (spleen, kidneys, epididymides, testes, thyroid and thymus) still showed differences from controls at the end of recovery.

The significance of some of the observed organ weight variations (liver and thymus) was supported by macroscopic and microscopic findings.

5.11 Macroscopic observations (Table 11; Appendix 12)

Unscheduled death:
One group 2 female was found dead on day 23 of the study. The most relevant changes, observed at necropsy, were dark red contents in the abdominal cavity and 2 dark, ruptured areas in the liver.

Final sacrifice:
Pale colour of the liver, sometimes accompanied by swollen shape of the organ, was reported in 3/5 high dose and 1/5 mid-dose group males and in 1/5 high dose group females. Decreased size of the thymus was seen in 2/5 males from the high dose group. The seminal vesicles of 2/5 males from the same group appeared transparent.

Recovery sacrifice:
Enlargement of the liver and renal pelvis dilatation was recorded in 2/5 treated males.

5.12 Microscopic observations (Table 12; Appendix 12)

Unscheduled death:
The most important finding, observed in the found dead animal, was detected in the liver, where multifocal, mild haemorrhages were reported. This finding, along with the macroscopic observation in the abdominal cavity, suggests that this death could be considered spontaneous or accidental in origin.

Final sacrifice:
Changes, possibly related to the treatment, were noted in the liver, lungs and thymus of treated animals when compared to controls.
Liver: hepatocytic hypertrophy was observed in all high dose group animals, all mid-dose males and 4/5 low dose males. This finding showed mainly a panlobular distribution in the high dose group males, while it was limited to the centrilobular, mid-zonal areas in the remaining main phase animals.
Lungs: aggregation of alveolar macrophages was seen in the lungs of 4/5 males and 2/5 females from the high dose group. Such a finding could be possibly suggestive of a phospholipidosis.
No changes were observed in the spleen and kidneys.
Thymus: slight to moderate atrophy was observed in 3/5 males and in 1 female from the high dose group.

Recovery sacrifice:
Only a partial remission of the changes considered related to the administration of the test item was observed following the 2-week recovery period.
Liver: hepatocytic hypertrophy was still evident in all treated animals.
Lungs: instances of focal aggregation of alveolar macrophages were seen in the lungs of 1 treated male and 1 treated female.
Thymus: moderate atrophy was observed in 1 treated male.

Other findings:
Colloid depletion was observed in the seminal vesicles of 3/5 high dose group males. Hepatocytic necrosis was observed in 2/5 high dose and 1/5 intermediate dose males in the main phase and in 1 treated male from the recovery group. Due to the lack of a zonal distribution and being present in a few treated animals, this finding was considered spontaneous in origin. The above changes, as well as the moderate chronic inflammation reported in the liver of 1 high dose male killed at termination of the treatment phase, were considered to be unspecific, possibly linked to the general condition of the treated animals and spontaneous in origin.

The remaining findings reported in the animals sacrificed after completion of the scheduled test periods and in the unscheduled dead animal were considered to be incidental or spontaneous in origin.

6. CONCLUSION

The oral toxicity of [redacted] when given by daily administration to rats at dosages of 0.3, 0.8 and 2.0 mg/kg/day has been investigated over a period of 4 weeks and possible recovery from any treatment-related changes over a 2 week recovery period.

Animals dosed at 2 mg/kg/day showed no significant reactions during the in-life phase of the study. A slight but dose-related reduction of the grip strength was observed at neurological tests performed at the end of treatment, mainly for males. Slight reductions in body weight and food intake were noted in the males from this group at the end of treatment and recovery periods. A reduction in the WBC count (neutrophils and/or lymphocytes) was observed at the end of treatment and recovery periods. In addition, the prothrombin time was slightly increased in the males. Clinical chemistry investigations showed a dose-related alteration of the liver function in the males at the end of treatment (increases in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and total bilirubin, decrement of total protein, globulin and albumin). Alkaline phosphatase was still increased at the end of recovery period. Alanine aminotransferase and aspartate aminotransferase were completely recovered at the end of the treatment-free period. These increases were usually dose-related and, occasionally, outside the range of historical data. No significant hepatic marker alterations were observed in females. Other clinical chemistry parameters (urea, chloride, inorganic phosphorus and sodium) showed changes at the end of treatment, mainly in the males. At the end of the recovery period, no complete reversibility of such changes was observed. The cause of these changes however remains unclear and could not be conclusively attributed to the test item.
Absolute and relative liver weights were increased at this dose level in the males. Increments in the relative kidneys, testes and thyroid weights were observed at the end of the treatment period. Thymus and spleen relative and absolute weights were also statistically significantly reduced in the males at the end of treatment. These changes were not reversible at the end of recovery. Females of this dose group showed increments in absolute and relative liver weights and decrement of the spleen weight (both absolute and relative), without recovery.
The toxicological significance of the changes observed in the liver was definitely supported by the findings reported at *post mortem* examination. Pale colour of the liver, sometimes accompanied by swollen shape of the organ, was reported in the majority of the males and in individual females. Decreased size of the thymus was also seen in the high dose animals (mainly in the males).
Treatment-related changes were noted at microscopic examination in the liver, lungs and thymus. The liver was the most affected organ. Hepatocytic hypertrophy suggestive of an adaptive change was observed in animals from this dose group. The observed findings were of lower severity and incidence in the females.
Thymus atrophy was also observed in the high dose animals. This lesion showed a higher severity degree in the males, when compared to female animals and along with the colloid depletion in the animal vesicles noted in some high dose males it could be considered secondary to the poor general condition of the animals.
Aggregation of alveolar macrophages was seen in the lungs of males and females. Such a finding could be possibly suggestive of a phospholipidosis condition. No histopathological effects were observed in the spleen and kidneys.

In animals dosed at 0.8 mg/kg/day, the toxicological systemic effects were less relevant than for animals of the high dose group. A reduction of the grip strength was observed both in males and in females. No significant reductions in body weight and food consumption were observed for either sexes.

Slight effects in the haematological parameters, such as a decrease in the white blood cell count, were seen in female animals. Clinical chemistry variations, mainly comprising increment of alkaline phosphatase, alanine aminostranferase and aspartate aminotransferase were noted only in males. No significant hepatic marker alterations were observed in the females.
Absolute and relative liver weights were increased in the males, along with decrease in spleen and thymus weights. Females showed increment in liver and decrement in spleen weights both for the absolute and relative values.
The microscopic examination revealed liver hepatocytic hypertrophy in all the males but not in the females. No histopathological effects were observed in the spleen.

At 0.3 mg/kg/day, "in-life" observations showed a reduction in grip strength in the males. No effects in body weight and food consumption, haematological and clinical chemistry parameters were seen in these animals. Absolute and relative liver weight increment, along with decrement in spleen weight was still evident. Microscopic pathology revealed hepatocytic hypertrophy in the majority of male animals.
The only effect observed in the females was a slight decrease in spleen relative and absolute weights. No histopathological effects were observed in this organ.

On the basis of these results, signs of an evident toxic effect of the test item were seen at the 2 higher dose levels (0.8 and 2.0 mg/kg/day). Most of the observed effects were not reversible over a 2 week recovery period in the high dose animals. The findings in the liver, observed at all the doses were a clear indication of a toxic effect of the test item to this organ. Males were clearly more sensitive than females. Also the toxicokinetic half-life values were higher in males than females. Detectable plasma levels of the [redacted] were measured between 2 and 216 hours after dosing the animals at 2 mg/kg. C_{max} was usually measured after 24 hours post-dose (T_{max}), even though for some fractions different T_{max} were calculated, usually in the females. Due to the high plasma levels recorded at 216 hours post-dose, a correct calculation of the half-life (T ½) was not possible, only estimations were performed, comprised in the range of 201-544 hours for males and 39-763 hours for females. This situation did not allow the calculation of a significant value of the AUC.
Effects on the main target organ, the liver, although at a lower incidence when compared to those observed at the higher dose levels, were also observed in the males of the low dose level (0.3 mg/kg/day). Besides changes in the liver, only minor effects were observed at 0.3 mg/kg/day in the males. The majority of these effects were not considered adverse, as they slight, often not dose-related and within the normal range of historical control data. The hepatocytic hypertrophy could be suggestive of an adaptive change. However, the lack of recovery over a 2 week treatment-free period, seen in the high-dose animals, may be an indication of other changes occurring in the liver, not detectable through the standard microscopic examination. Therefore, none of the dose levels investigated may be considered either a No Observed Effect Level (NOEL) or a No Observed Adverse Effect Level (NOAEL) in this study for males. On the contrary, females appeared to be less sensitive than males. At 0.3 mg/kg/day no adverse effects were observed. Therefore this dose can be considered a No Observed Adverse Effect Level (NOAEL) for the females.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FIGURE 1 - Group and cage arrangement on battery

STUDY NO.: [redacted]

MAIN PHASE

Group Number:	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
1	0.0	Control	2 - 10	1 - 9	1	7
2	0.3	Low	22 - 30	21 - 29	3	9
3	0.8	Medium	32 - 40	31 - 39	4	10
4	2.0	High	42 - 50	41 - 49	5	11
+: in terms of test item as supplied						

RECOVERY PHASE

Group Number:	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
1	0.0	Control	12 - 20	11 - 19	2	8
4	2.0	High	52 - 60	51 - 59	6	12
+: in terms of test item as supplied °: No treatment will be given during the recovery period.						

MAIN PHASE

Group/Sex
Cage no.

Males		Females	
1M	4M^{R}	1F	4F^{R}
1	6	7	12
2M		2F	
3		9	
3M		3F	
4		10	
4M		4F	
5		11	
1M^{R}		1F^{R}	
2		8	

^{R} = Recovery

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FIGURE 1 - Group and cage arrangement on battery (continued)

STUDY NO. [redacted]

SATELLITE GROUP

Group Number:	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
5	2.0	High	62 – 78	61 - 77	13-15	16-18
+: in terms of test item as supplied						

Group/Sex
Cage no.

Males	Females
5M 13	5F 16
5M 14	5F 17
5M 15	5F 18

Group/Sex
Cage no.

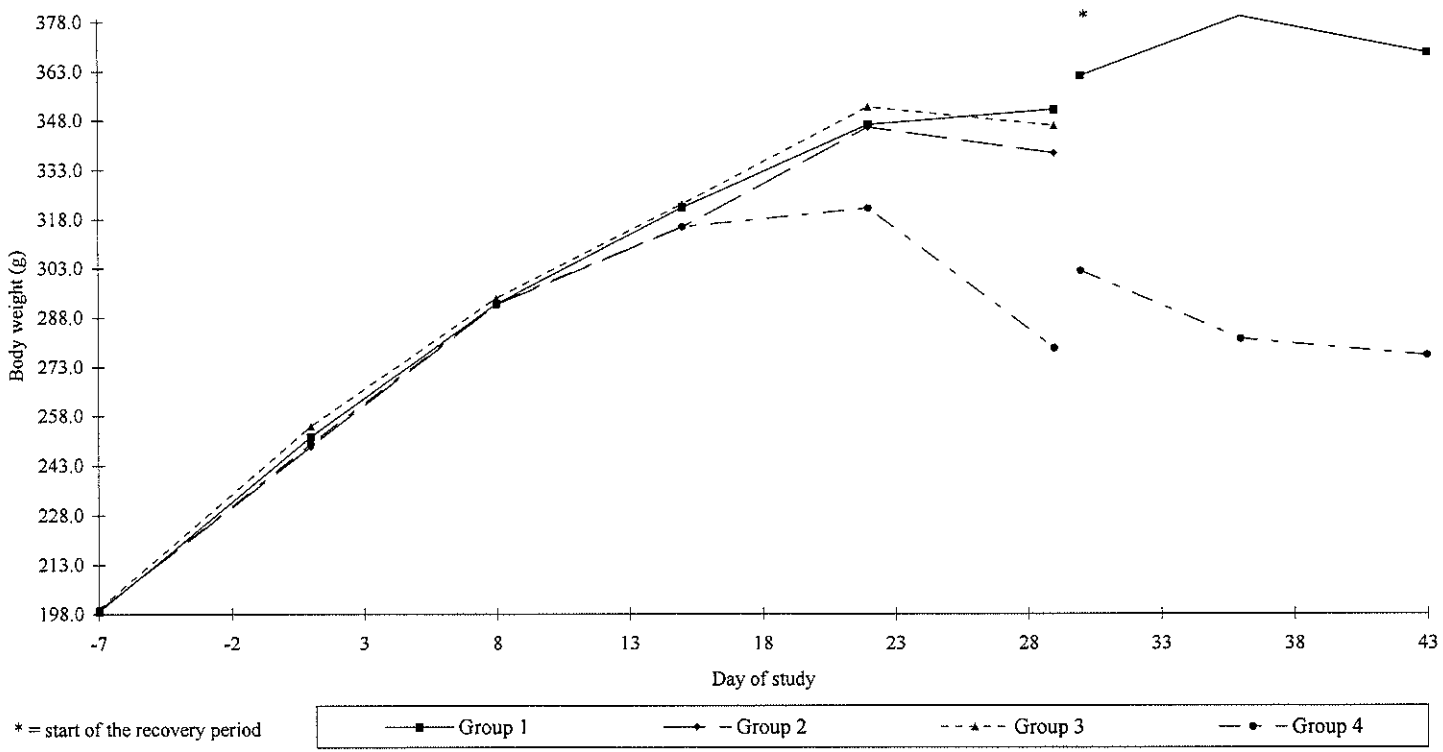
Males	Females
$1M^R$ 2	
$4M^R$ 6	
	$1F^R$ 8
	$4F^R$ 12

^{R} = Recovery

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FIGURE 2.1 - Body weight versus day of study - Males

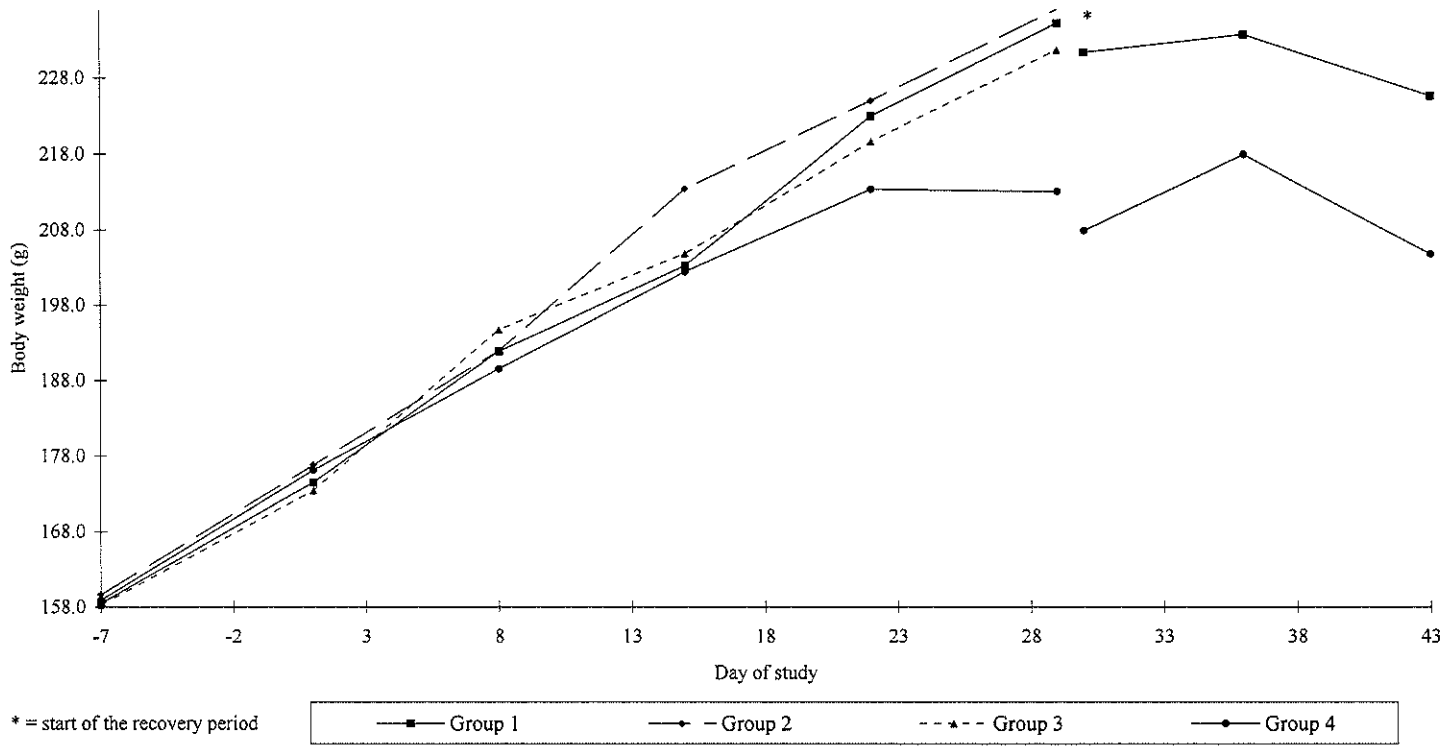
STUDY NO.: [redacted]



[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FIGURE 2.2 - Body weight versus day of study - Females

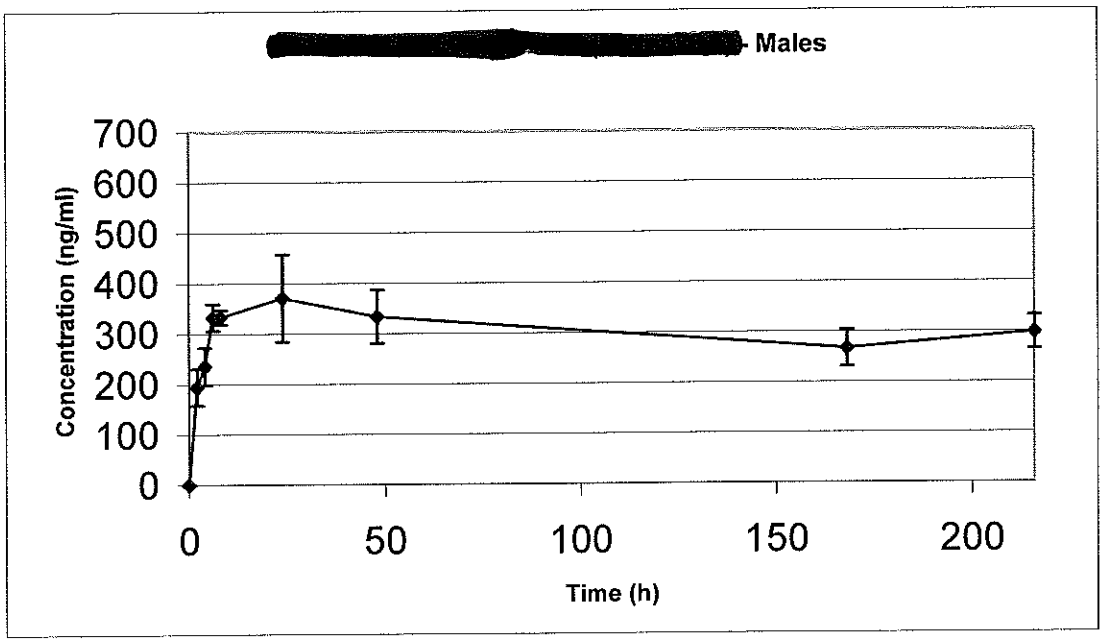
STUDY NO.: [redacted]



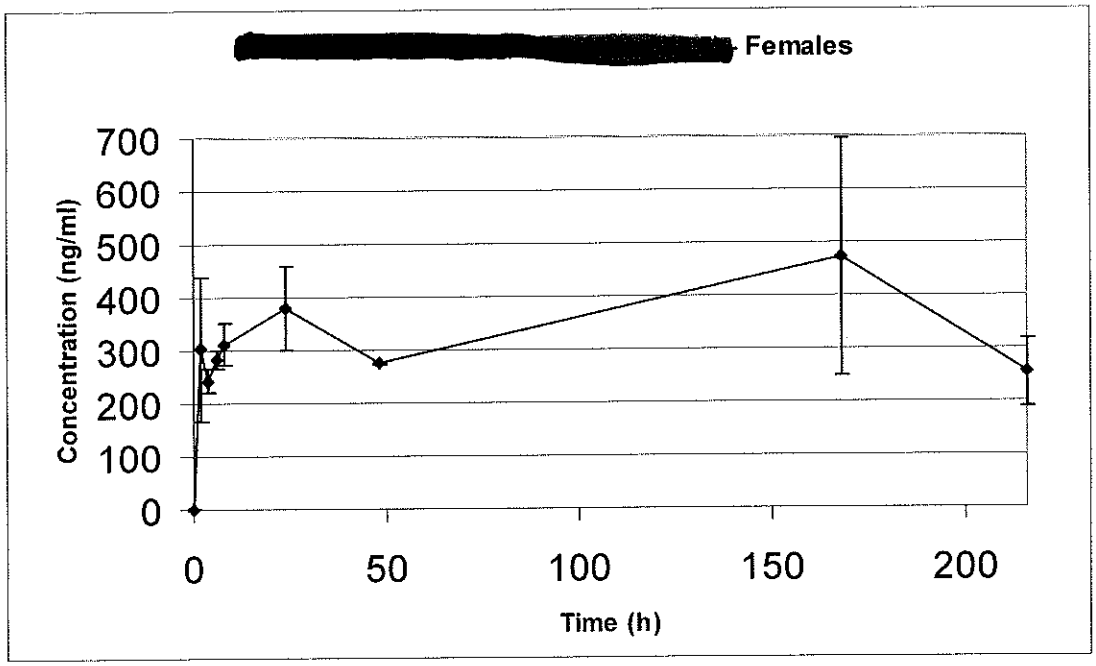
[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FIGURE 3 - [redacted] - Plasma levels

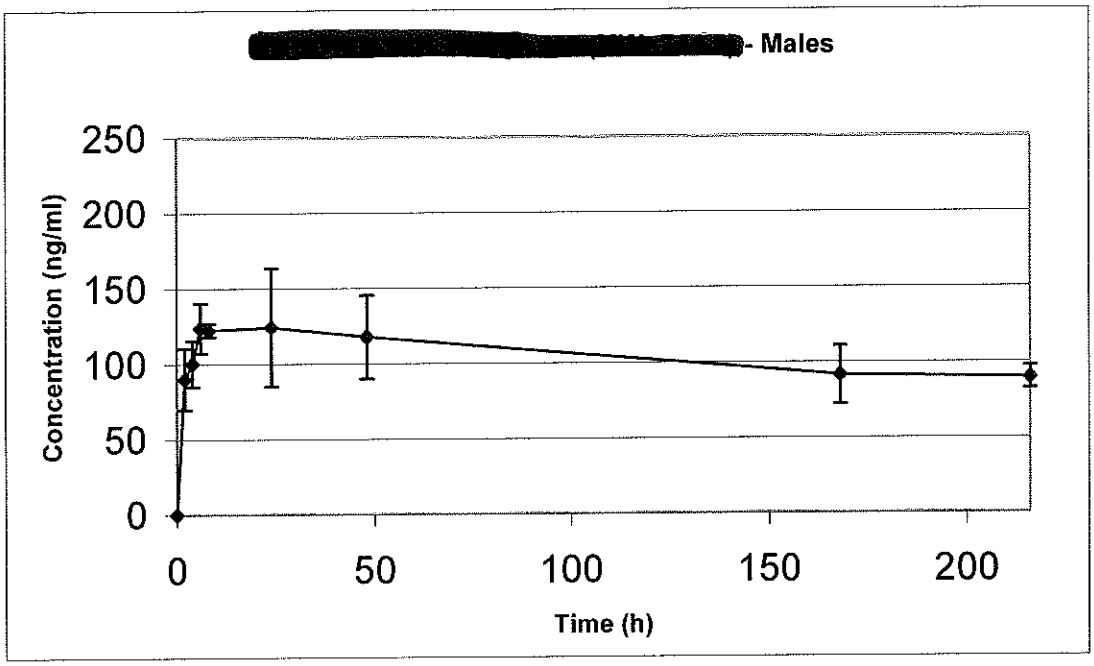
STUDY NO.: [redacted]



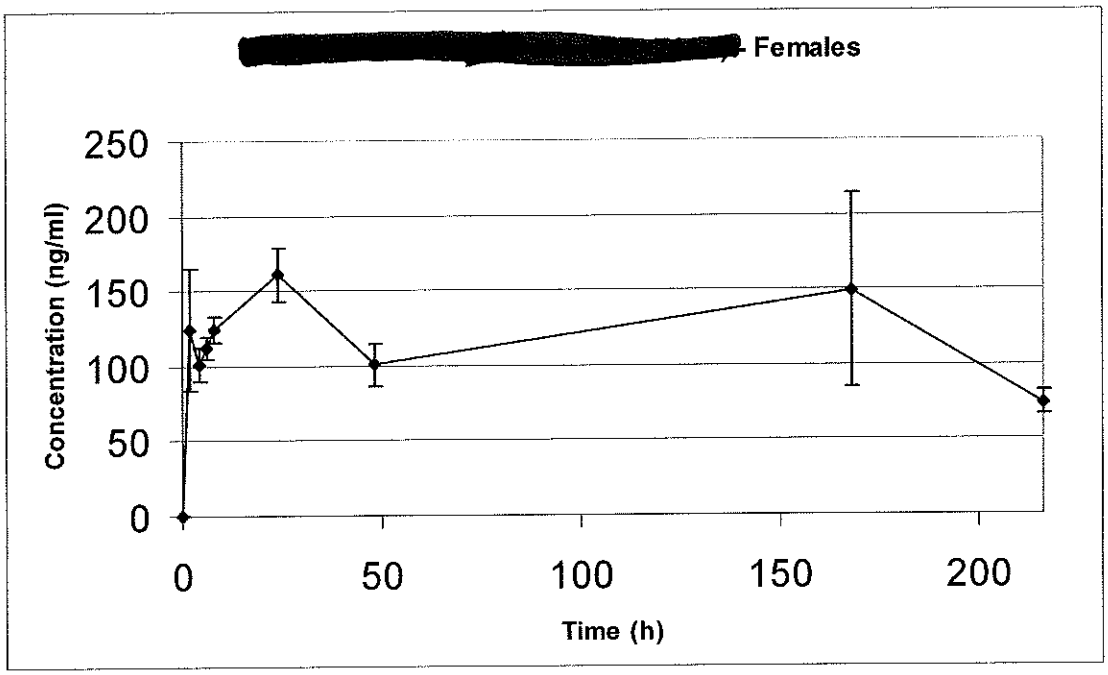
T_{max} (h): 24 T ½ (h): 544 AUC (24-216) (ng/ml·h): 65550
C_{max} (ng/ml): 370.2 AUC (inf) (ng/ml·h): 299662



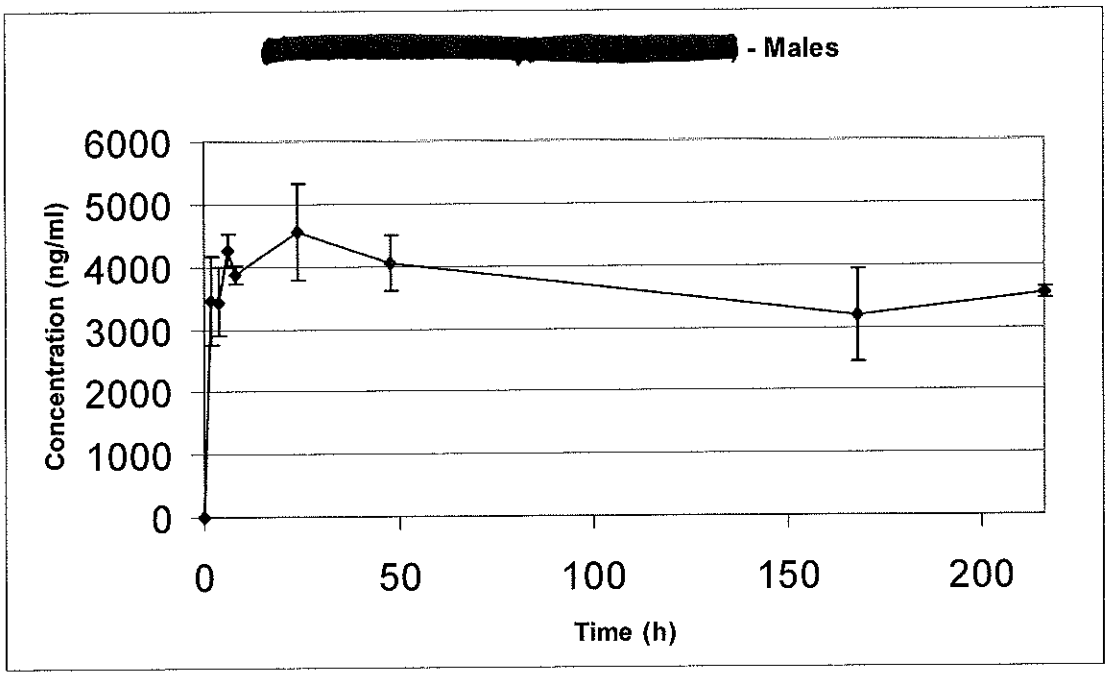
T_{max} (h): 168 T ½ (h): 2185 AUC (24-216) (ng/ml·h): 77653
C_{max} (ng/ml): 472.5 AUC (inf) (ng/ml·h): 877949



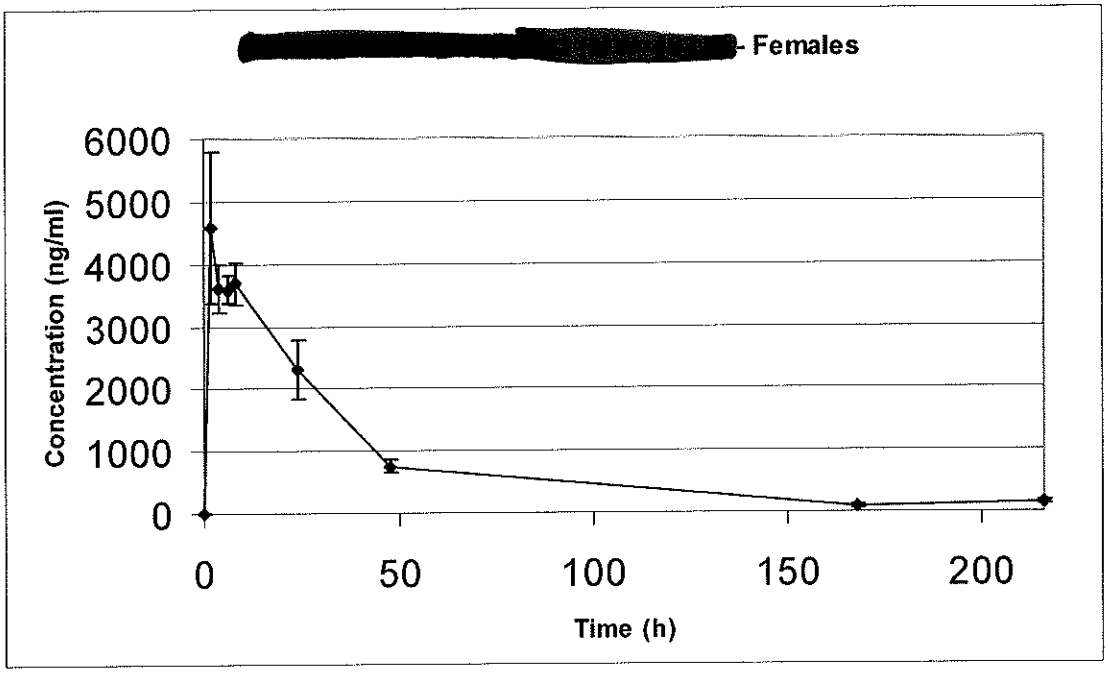
T_{max} (h): 24 T ½ (h): 385 AUC (24-216) (ng/ml·h): 22516
C_{max} (ng/ml): 124.3 AUC (inf) (ng/ml·h): 72388



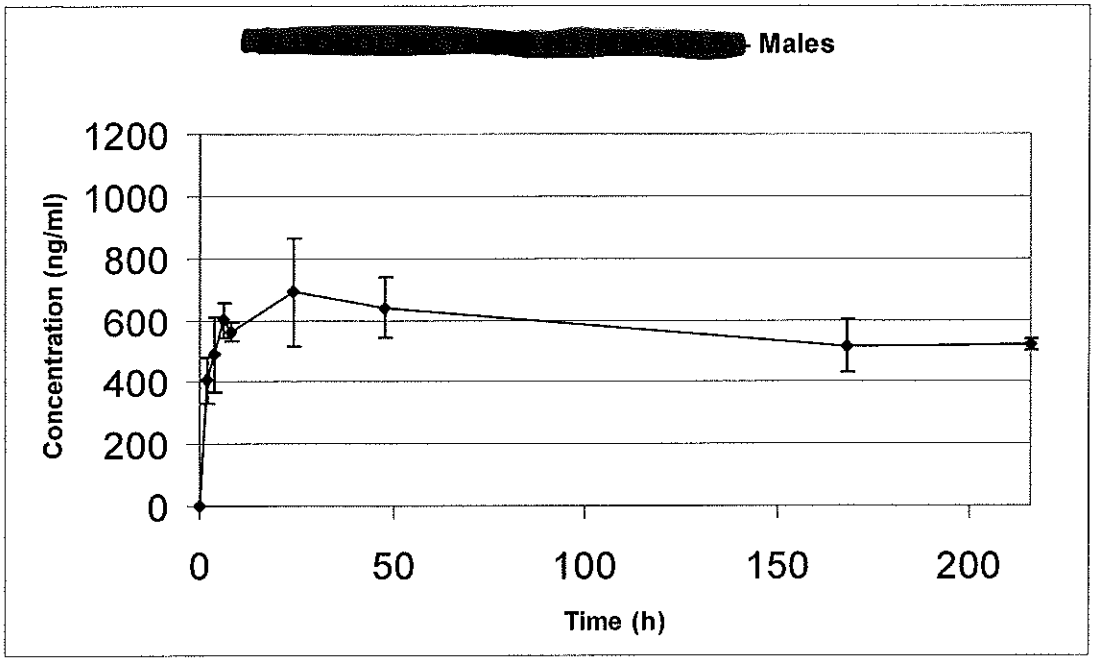
T_{max} (h): 24 T ½ (h): 346 AUC (24-216) (ng/ml·h): 26563
C_{max} (ng/ml): 160.7 AUC (inf) (ng/ml·h): 63751



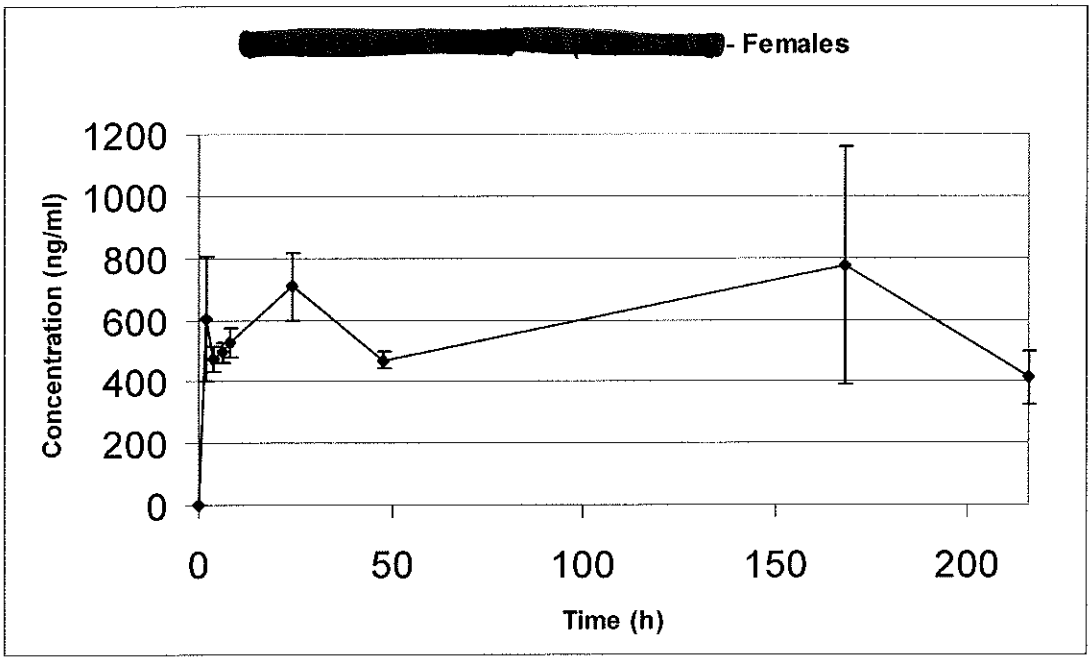
T_{max} (h): 24 T ½ (h): 481 AUC (24-216) (ng/ml·h): 791984
C_{max} (ng/ml): 4545.4 AUC (inf) (ng/ml·h): 3249932



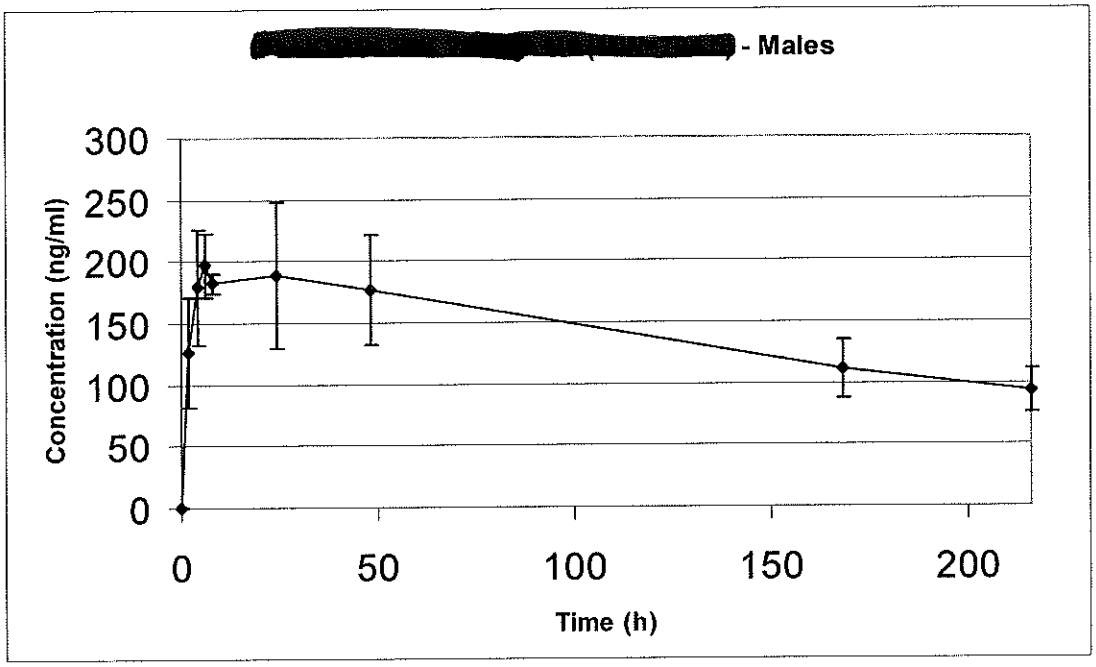
T_{max} (h): 2 T ½ (h): 39 AUC (2-216) (ng/ml·h): 167950
C_{max} (ng/ml): 4581.3 AUC (inf) (ng/ml·h): 176042



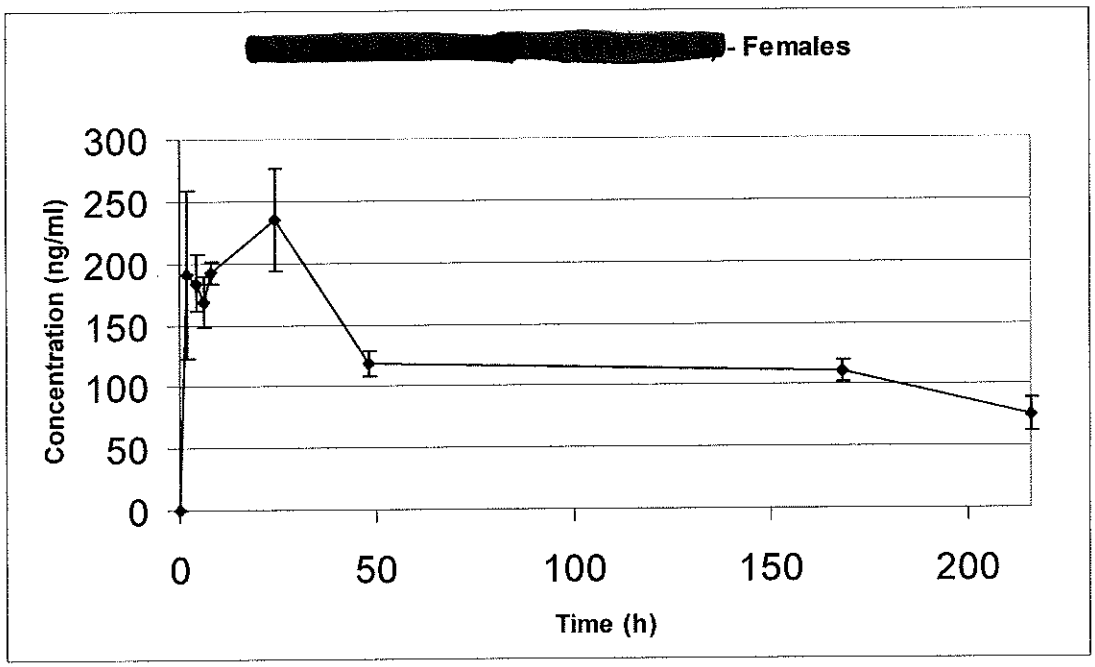
T_{max} (h): 24 T ½ (h): 454 AUC (24-216) (ng/ml·h): 123729
C_{max} (ng/ml): 689.3 AUC (inf) (ng/ml·h): 464508



T_{max} (h): 168 T ½ (h): 763 AUC (24-216) (ng/ml·h): 130770
C_{max} (ng/ml): 773.8 AUC (inf) (ng/ml·h): 584697



T_{max} (h): 6 T ½ (h): 201 AUC (6-216) (ng/ml·h): 30768
C_{max} (ng/ml): 196.9 AUC (inf) (ng/ml·h): 57915



T_{max} (h): 24 T ½ (h): 160 AUC (24-216) (ng/ml·h): 27116
C_{max} (ng/ml): 234.7 AUC (inf) (ng/ml·h): 44431

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: [redacted]

MALES

Interval: 1 - 4 Weeks Group Observation	1 (10)		2 (5)		3 (5)		4 (10)	
	a	b	a	b	a	b	a	b
APPEARANCE								
Staining	1	2.0	0	0.0	0	0.0	0	0.0
Hairloss	1	1.0	0	0.0	1	1.0	0	0.0
REMOVAL								
Removal easy	10	4.0	5	4.0	5	4.0	10	4.0
HANDLING REACTIVITY								
Handling reactivity normal	10	4.0	5	4.0	5	4.0	10	4.0
LACHRYMATION								
Lachrymation absent	10	4.0	5	4.0	5	4.0	10	4.0
PALPEBRAL CLOSURE								
Palpebral closure absent	10	4.0	5	4.0	5	4.0	10	4.0
SALIVATION								
Salivation absent	10	4.0	5	4.0	5	4.0	10	4.0
PILOERECTION								
Piloerection absent	10	4.0	5	4.0	5	4.0	10	4.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: [redacted]

MALES

Interval: 1 - 4 Weeks Group Observation	1 (10)		2 (5)		3 (5)		4 (10)	
	a	b	a	b	a	b	a	b
REARING								
Rearing absent	1	1.0	0	0.0	0	0.0	0	0.0
Rearing 1-3	2	1.0	1	1.0	0	0.0	0	0.0
Rearing 4-7	9	1.1	4	1.0	0	0.0	2	1.5
Rearing 8-10	4	1.3	3	1.0	3	1.0	5	1.2
Rearing 11-14	2	1.0	3	1.3	3	1.0	7	1.6
Rearing 15-20	8	1.4	3	1.7	5	2.2	6	2.2
Rearing 21-30	6	1.2	1	3.0	1	2.0	5	1.2
Rearing more than 30	2	1.0	0	0.0	1	1.0	1	1.0
SPASMS								
Spasms absent	10	4.0	5	4.0	5	4.0	10	4.0
MYOCLONIA								
Myoclonia absent	10	4.0	5	4.0	5	4.0	10	4.0
GAIT								
Normal gait	10	4.0	5	4.0	5	4.0	10	4.0
MOBILITY IMPAIRMENT								
Mobility impairment absent	10	4.0	5	4.0	5	4.0	10	4.0
AROUSAL								
Arousal normal	10	4.0	5	4.0	5	4.0	10	4.0
VOCALISATION								
Vocalisation absent	10	4.0	5	4.0	5	4.0	10	4.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: [redacted]

MALES

Interval: 1 - 4 Weeks Group Observation	1 (10)		2 (5)		3 (5)		4 (10)	
	a	b	a	b	a	b	a	b
STEREOTYPIES								
Stereotypies absent	10	4.0	5	4.0	5	4.0	10	4.0
UNUSUAL RESPIRATION								
Unusual respiration absent	10	4.0	5	4.0	5	4.0	10	4.0
BIZARRE BEHAVIOUR								
Bizarre behaviour absent	10	4.0	5	4.0	5	4.0	10	4.0
URINATION								
Urination absent	8	1.6	3	2.7	2	1.5	7	1.9
Urination 1-3	9	1.4	4	2.0	4	2.3	7	2.1
Urination 4-6	8	1.3	1	1.0	1	1.0	3	1.0
Urination 7-9	1	1.0	1	1.0	3	1.0	3	1.7
Urination more than 10	2	1.5	1	2.0	2	2.0	4	1.0
DEFECATION								
Defecation absent	10	3.9	5	3.6	5	4.0	10	4.0
Defecation 1-3	1	1.0	0	0.0	0	0.0	0	0.0
Defecation 4-6	0	0.0	1	2.0	0	0.0	0	0.0
TREMORS								
Tremors absent	10	4.0	5	4.0	5	4.0	10	4.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: [redacted]

FEMALES

Interval: 1 - 4 Weeks

Group	1		2		3		4	
Observation	(10)		(5)		(5)		(10)	
	a	b	a	b	a	b	a	b
REMOVAL								
Removal easy	10	4.0	5	3.8	5	4.0	10	4.0
HANDLING REACTIVITY								
Handling reactivity normal	10	4.0	5	3.8	5	4.0	10	4.0
LACHRYMATION								
Lachrymation absent	10	4.0	5	3.8	5	4.0	10	4.0
PALPEBRAL CLOSURE								
Palpebral closure absent	10	4.0	5	3.8	5	4.0	10	4.0
SALIVATION								
Salivation absent	10	4.0	5	3.8	5	4.0	10	4.0
PILOERECTION								
Piloerection absent	10	4.0	5	3.8	5	4.0	10	4.0
REARING								
Rearing 1-3	0	0.0	0	0.0	0	0.0	1	1.0
Rearing 4-7	1	1.0	0	0.0	0	0.0	0	0.0
Rearing 8-10	1	1.0	0	0.0	0	0.0	0	0.0
Rearing 11-14	1	2.0	0	0.0	1	1.0	0	0.0
Rearing 15-20	1	2.0	1	1.0	1	2.0	1	3.0
Rearing 21-30	6	2.7	4	2.5	4	2.8	9	3.1
Rearing more than 30	7	2.6	3	2.7	5	1.2	5	1.6

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: [redacted]

FEMALES

Interval: 1 - 4 Weeks Group Observation	1 (10)		2 (5)		3 (5)		4 (10)	
	a	b	a	b	a	b	a	b
SPASMS								
Spasms absent	10	4.0	5	3.8	5	4.0	10	4.0
MYOCLONIA								
Myoclonia absent	10	4.0	5	3.8	5	4.0	10	4.0
GAIT								
Normal gait	10	4.0	5	3.8	5	4.0	10	4.0
MOBILITY IMPAIRMENT								
Mobility impairment absent	10	4.0	5	3.8	5	4.0	10	4.0
AROUSAL								
Arousal normal	10	4.0	5	3.8	5	4.0	10	4.0
VOCALISATION								
Vocalisation absent	10	4.0	5	3.8	5	4.0	10	4.0
STEREOTYPIES								
Stereotypies absent	10	4.0	5	3.8	5	4.0	10	4.0
UNUSUAL RESPIRATION								
Unusual respiration absent	10	4.0	5	3.8	5	4.0	10	4.0
BIZARRE BEHAVIOUR								
Bizarre behaviour absent	10	4.0	5	3.8	5	4.0	10	4.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.1 - Clinical signs - During treatment - Group incidence

STUDY NO.: [redacted]

FEMALES

Interval: 1 - 4 Weeks

Group	1		2		3		4	
Observation	(10)		(5)		(5)		(10)	
	a	b	a	b	a	b	a	b
URINATION								
Urination absent	10	3.2	5	2.8	5	3.6	10	3.5
Urination 1-3	4	1.5	3	1.7	2	1.0	5	1.0
Urination 4-6	1	2.0	0	0.0	0	0.0	0	0.0
DEFECATION								
Defecation absent	10	4.0	5	3.8	5	4.0	10	4.0
TREMORS								
Tremors absent	10	4.0	5	3.8	5	4.0	10	4.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: [redacted]

MALES

Interval: 1 - 2 Weeks Group Observation	1 (5)		4 (5)	
	a	b	a	b
APPEARANCE				
Scab(s)	0	0.0	1	1.0
Hairloss	0	0.0	3	1.0
REMOVAL				
Removal easy	5	2.0	5	2.0
HANDLING REACTIVITY				
Handling reactivity normal	5	2.0	5	2.0
LACHRYMATION				
Lachrymation absent	5	2.0	5	2.0
PALPEBRAL CLOSURE				
Palpebral closure absent	5	2.0	5	2.0
SALIVATION				
Salivation absent	5	2.0	5	2.0
PILOERECTION				
Piloerection absent	5	2.0	5	2.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: [redacted]

MALES

Interval: 1 - 2 Weeks Group Observation	1 (5)		4 (5)	
	a	b	a	b
REARING				
Rearing 1-3	1	1.0	1	1.0
Rearing 4-7	2	1.0	1	1.0
Rearing 8-10	1	2.0	4	1.0
Rearing 11-14	2	1.5	3	1.0
Rearing 15-20	0	0.0	1	1.0
Rearing 21-30	1	2.0	0	0.0
SPASMS				
Spasms absent	5	2.0	5	2.0
MYOCLONIA				
Myoclonia absent	5	2.0	5	2.0
GAIT				
Normal gait	5	2.0	5	2.0
MOBILITY IMPAIRMENT				
Mobility impairment absent	5	2.0	5	2.0
AROUSAL				
Arousal normal	5	2.0	5	2.0
VOCALISATION				
Vocalisation absent	5	2.0	5	2.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: [redacted]

MALES

Interval: 1 - 2 Weeks Group Observation	1 (5)		4 (5)	
	a	b	a	b
STEREOTYPIES				
Stereotypies absent	5	2.0	5	2.0
UNUSUAL RESPIRATION				
Unusual respiration absent	5	2.0	5	2.0
BIZARRE BEHAVIOUR				
Bizarre behaviour absent	5	2.0	5	2.0
URINATION				
Urination absent	1	1.0	1	2.0
Urination 1-3	2	1.0	4	2.0
Urination 4-6	4	1.0	0	0.0
Urination 7-9	1	1.0	0	0.0
Urination more than 10	2	1.0	0	0.0
DEFECATION				
Defecation absent	5	2.0	5	2.0
TREMORS				
Tremors absent	5	2.0	5	2.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: [redacted]

FEMALES

Interval: 1 - 2 Weeks Group Observation	1 (5)		4 (5)	
	a	b	a	b
REMOVAL				
Removal easy	5	2.0	5	2.0
HANDLING REACTIVITY				
Handling reactivity normal	5	2.0	5	2.0
LACHRYMATION				
Lachrymation absent	5	2.0	5	2.0
PALPEBRAL CLOSURE				
Palpebral closure absent	5	2.0	5	2.0
SALIVATION				
Salivation absent	5	2.0	5	2.0
PILOERECTION				
Piloerection absent	5	2.0	5	2.0
REARING				
Rearing 11-14	0	0.0	1	1.0
Rearing 15-20	0	0.0	3	1.0
Rearing 21-30	4	1.3	4	1.5
Rearing more than 30	4	1.3	0	0.0
SPASMS				
Spasms absent	5	2.0	5	2.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: [redacted]

FEMALES

Interval: 1 - 2 Weeks Group Observation	1 (5)		4 (5)	
	a	b	a	b
MYOCLONIA				
Myoclonia absent	5	2.0	5	2.0
GAIT				
Normal gait	5	2.0	5	2.0
MOBILITY IMPAIRMENT				
Mobility impairment absent	5	2.0	5	2.0
AROUSAL				
Arousal normal	5	2.0	5	2.0
VOCALISATION				
Vocalisation absent	5	2.0	5	2.0
STEREOTYPIES				
Stereotypies absent	5	2.0	5	2.0
UNUSUAL RESPIRATION				
Unusual respiration absent	5	2.0	5	2.0
BIZARRE BEHAVIOUR				
Bizarre behaviour absent	5	2.0	5	2.0
URINATION				
Urination absent	5	1.4	5	1.6
Urination 1-3	3	1.0	2	1.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 1.2 - Clinical signs - During recovery - Group incidence

STUDY NO.: [redacted]

FEMALES

Interval: 1 - 2 Weeks Group Observation	1 (5)		4 (5)	
	a	b	a	b
DEFECATION				
Defecation absent	5	2.0	5	2.0
TREMORS				
Tremors absent	5	2.0	5	2.0

Key: () = Number of animals alive at start of interval
a = Number of animals affected
b = Number of weeks with clinical sign/animal

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 2.1 - Motor activity - At the end of treatment - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
Counter display	904.6	208.0	10	925.6	198.7	5	1142.2	271.9	5	846.1	322.2	10

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 2.1 - Motor activity - At the end of treatment - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
Counter display	1027.1	145.6	10	922.8	126.9	4	956.6	67.5	5	936.0	171.9	10

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 2.2 - Motor activity - At the end of recovery - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
Counter display	930.4	280.1	5	864.2	241.7	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 2.2 - Motor activity - At the end of recovery - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
Counter display	979.8	159.9	5	929.0	96.8	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 3.1 - Body weight (g) - During treatment - Group mean data

STUDY NO.: [redacted]

MALES

Group(s)		Day of Phase 1!	1"	8	15	22	29
1	(n)	10	10	10	10	10	5
	Mean	198.83	251.67	292.10	321.58	346.56	351.08
	SD	5.93	5.66	8.36	11.81	11.76	9.58
2	(n)	5	5	5	5	5	5
	Mean	199.35	248.83	291.84	315.54	345.82	337.91
	SD	7.28	7.73	10.09	14.11	16.90	14.31
3	(n)	5	5	5	5	5	5
	Mean	199.71	254.91	293.88	322.67	351.92	346.24
	SD	5.33	6.07	3.67	9.03	7.66	11.27
4	(n)	10	10	10	10	10	5
	Mean	199.33	249.58	292.24	315.66	321.36**	278.69**
	SD	7.04	7.46	8.61	12.27	16.25	24.70

Note: ! = Pretest phase; " = Dosing phase;
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 3.1 - Body weight (g) - During treatment - Group mean data

STUDY NO.: [redacted]

FEMALES

Group(s)		Day of Phase 1!	1"	8	15	22	29
1	(n)	10	10	10	10	10	5
	Mean	158.51	174.55	191.88	203.24	222.92	235.19
	SD	5.88	11.36	12.24	9.53	12.14	10.93
2	(n)	5	5	5	5	5	4
	Mean	159.66	176.80	191.97	213.44	224.97	237.02
	SD	6.66	8.07	10.83	10.67	10.19	6.18
3	(n)	5	5	5	5	5	5
	Mean	158.28	173.42	194.78	204.80	219.57	231.64
	SD	6.18	7.53	13.99	13.53	10.97	13.29
4	(n)	10	10	10	10	10	5
	Mean	158.92	176.11	189.75	202.43	213.40	213.07**
	SD	6.30	7.27	10.54	6.89	10.26	7.70

Note: ! = Pretest phase; " = Dosing phase;
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett's test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 3.2 - Body weight (g) - During recovery - Group mean data

STUDY NO.: [redacted]

MALES

Group(s)		Day of Phase 1	8	15
1	(n)	5	5	5
	Mean	361.56	379.63	368.60
	SD	14.45	16.96	19.32
4	(n)	5	5	5
	Mean	302.16**	281.52**	276.64**
	SD	11.63	36.96	32.49

Note: Data for Recovery phase
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 3.2 - Body weight (g) - During recovery - Group mean data

STUDY NO.: [redacted]

FEMALES

Group(s)		Day of Phase 1	8	15
1	(n)	5	5	5
	Mean	231.34	233.68	225.59
	SD	9.42	11.63	8.92
4	(n)	5	5	5
	Mean	207.92**	217.92*	204.76**
	SD	7.53	9.52	8.87

Note: Data for Recovery phase
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 4.1 - Body weight change° (g) - During treatment - Group mean data

STUDY NO.: [redacted]

MALES

Group(s)		Day of Phase 8!	15	22	29
1	(n)	10	10	10	5
	Mean	40.42	69.91	94.89	95.83
	SD	6.66	9.66	11.31	11.20
2	(n)	5	5	5	5
	Mean	43.01	66.71	96.99	89.07
	SD	3.97	8.55	9.59	8.14
3	(n)	5	5	5	5
	Mean	38.98	67.76	97.01	91.34
	SD	2.78	8.79	11.62	13.00
4	(n)	10	10	10	5
	Mean	42.66	66.08	71.78**	27.26**
	SD	5.78	10.74	16.62	26.92

Note: ! = Dosing phase; " = Recovery phase
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
° = mean body weight change relevant to Day 1 of study

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 4.1 - Body weight change° (g) - During treatment - Group mean data

STUDY NO.: [redacted]

FEMALES

Group(s)		Day of Phase 8!	15	22	29
1	(n)	10	10	10	5
	Mean	17.33	28.69	48.37	52.12
	SD	4.39	7.18	9.01	8.76
2	(n)	5	5	5	4
	Mean	15.17	36.64	48.17	57.59
	SD	4.48	6.86	10.46	4.66
3	(n)	5	5	5	5
	Mean	21.36	31.38	46.15	58.22
	SD	10.75	10.05	9.02	12.87
4	(n)	10	10	10	5
	Mean	13.63	26.32	37.29*	38.67
	SD	9.45	6.11	10.84	7.99

Note: ! = Dosing phase; " = Recovery phase
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
° = mean body weight change relevant to Day 1 of study

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 4.2 - Body weight change° (g) - During recovery - Group mean data

STUDY NO.: [redacted]

MALES

Group(s)		Day of Phase 1	Day of Phase 8	Day of Phase 15
1	(n)	5	5	5
	Mean	113.46	131.53	120.5
	SD	13.52	15.94	18.09
4	(n)	5	5	5
	Mean	54.42**	33.78**	28.90**
	SD	16.72	43.25	40.11

Note: Data for Recovery phase
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
° = mean body weight change relevant to Day 1 of study

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 4.2 - Body weight change° (g) - During recovery - Group mean data

STUDY NO.: [redacted]

FEMALES

Group(s)		Day of Phase 1	Day of Phase 8	Day of Phase 15
1	(n)	5	5	5
	Mean	65.31	67.65	59.56
	SD	8.86	7.62	7.13
4	(n)	5	5	5
	Mean	30.11	40.11**	26.95
	SD	12.67	9.81	10.69

Note: Data for Recovery phase
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett's test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
° = mean body weight change relevant to Day 1 of study

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.1 - Haematology - At the end of treatment - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
RED BLOOD CELL COUNT 10^12/l	7.914	0.243	5	7.808	0.327	5	7.516	0.213	5	8.192	0.421	5
HAEMOGLOBIN g/dl	15.08	0.33	5	14.96	0.57	5	14.72	0.62	5	15.62	0.61	5
HAEMATOCRIT %	43.10	0.96	5	41.80	1.99	5	41.54	1.94	5	44.24	1.62	5
MEAN RED BLOOD CELL VOLUME fl	54.46	1.69	5	53.54	1.36	5	55.26	1.22	5	54.06	1.21	5
MEAN CORPUSCULAR Hb pg	19.08	0.60	5	19.20	0.45	5	19.60	0.41	5	19.10	0.31	5
MEAN CORPUSCULAR Hb CONC. g/dl	35.02	0.34	5	35.84*	0.49	5	35.48	0.23	5	35.32	0.45	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.1 - Haematology - At the end of treatment - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
PLATELETS 10^9/l	888.4	76.0	5	828.0	90.1	5	757.0*	61.5	5	876.2	63.3	5
PROTHROMBIN TIME sec	15.82	0.72	5	16.92*	0.66	5	16.12	0.43	5	17.98**	0.49	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.1 - Haematology - At the end of treatment - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
WHITE BLOOD CELL COUNT 10^9/l		8.414	0.724	5	8.778	1.296	5	8.164	2.609	5	6.824	0.671	5
NEUTROPHILS %		20.28	4.28	5	12.46*	3.91	5	16.42	4.59	5	14.50	5.64	5
LYMPHOCYTES %		75.00	3.70	5	81.48	3.33	5	77.92	4.68	5	78.30	6.92	5
MONOCYTES %		2.92	0.26	5	3.60	0.90	5	3.26	0.64	5	4.32	1.30	5
EOSINOPHILS %	($)	0.90	0.34	5	1.26	0.23	5	1.24	0.38	5	1.24	1.02	5
BASOPHILS %		0.20	0.07	5	0.20	0.07	5	0.34	0.13	5	0.62**	0.19	5
LARGE UNSTAINED CELLS %	($)	0.74	0.05	5	0.96	0.28	5	0.80	0.25	5	1.06	0.39	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.1 - Haematology - At the end of treatment - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
RED BLOOD CELL COUNT 10^12/l	6.996	0.303	5	7.090	0.104	4	7.128	0.153	5	7.066	0.288	5
HAEMOGLOBIN g/dl	13.64	0.56	5	14.03	0.17	4	14.00	0.31	5	13.76	0.46	5
HAEMATOCRIT %	37.50	1.76	5	38.58	0.43	4	38.44	0.88	5	38.06	1.35	5
MEAN RED BLOOD CELL VOLUME fl	53.62	0.94	5	54.38	0.83	4	53.98	1.05	5	53.90	1.49	5
MEAN CORPUSCULAR Hb pg	19.48	0.38	5	19.78	0.26	4	19.62	0.30	5	19.46	0.48	5
MEAN CORPUSCULAR Hb CONC. g/dl	36.36	0.42	5	36.35	0.30	4	36.34	0.51	5	36.14	0.51	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.1 - Haematology - At the end of treatment - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
PLATELETS 10^9/l	($)	743.0	414.9	4	994.0	65.5	4	905.2	58.6	5	822.2	44.9	5
PROTHROMBIN TIME sec		16.90	0.26	3	16.95	0.59	4	16.78	0.36	5	16.80	1.06	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.1 - Haematology - At the end of treatment - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
WHITE BLOOD CELL COUNT 10^9/l	($)	7.124	1.052	5	7.175	0.411	4	5.924	0.848	5	5.806	2.475	5
NEUTROPHILS %		9.48	4.09	5	12.48	3.60	4	11.50	3.84	5	8.88	1.61	5
LYMPHOCYTES %		85.06	3.73	5	81.00	4.66	4	81.96	3.25	5	85.50	1.41	5
MONOCYTES %		3.20	1.15	5	3.88	0.94	4	3.18	0.76	5	3.20	0.63	5
EOSINOPHILS %		1.44	0.22	5	1.63	0.40	4	2.34*	0.74	5	1.40	0.44	5
BASOPHILS %		0.14	0.05	5	0.15	0.06	4	0.16	0.05	5	0.16	0.05	5
LARGE UNSTAINED CELLS %		0.72	0.13	5	0.88	0.10	4	0.86	0.26	5	0.90	0.19	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.2 - Haematology - At the end of recovery - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
RED BLOOD CELL COUNT 10^12/l	8.236	0.166	5	7.502*	0.520	5
HAEMOGLOBIN g/dl	15.22	0.31	5	13.96*	0.92	5
HAEMATOCRIT %	42.80	0.99	5	37.90**	2.75	5
MEAN RED BLOOD CELL VOLUME fl	51.98	0.96	5	50.54	1.13	5
MEAN CORPUSCULAR Hb pg	18.46	0.23	5	18.64	0.29	5
MEAN CORPUSCULAR Hb CONC. g/dl	35.56	0.25	5	36.90**	0.70	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.2 - Haematology - At the end of recovery - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
PLATELETS 10^9/l	926.6	50.9	5	1080.4	183.0	5
PROTHROMBIN TIME sec	16.22	0.50	5	17.50*	0.80	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.2 - Haematology - At the end of recovery - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
WHITE BLOOD CELL COUNT 10^9/l	10.584	1.786	5	8.920	2.418	5
NEUTROPHILS %	13.66	5.70	5	11.72	8.20	5
LYMPHOCYTES %	81.20	6.51	5	83.02	8.86	5
MONOCYTES %	2.84	0.59	5	3.16	0.55	5
EOSINOPHILS %	1.42	0.75	5	1.08	0.24	5
BASOPHILS %	0.16	0.05	5	0.16	0.05	5
LARGE UNSTAINED CELLS %	0.76	0.13	5	0.84	0.11	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.2 - Haematology - At the end of recovery - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
RED BLOOD CELL COUNT 10^12/l	7.532	0.201	5	7.058*	0.263	5
HAEMOGLOBIN g/dl	14.40	0.43	5	13.50*	0.55	5
HAEMATOCRIT %	39.70	1.05	5	37.50*	1.43	5
MEAN RED BLOOD CELL VOLUME fl	52.68	0.54	5	53.12	0.54	5
MEAN CORPUSCULAR Hb pg	19.12	0.43	5	19.16	0.44	5
MEAN CORPUSCULAR Hb CONC. g/dl	36.28	0.58	5	36.02	0.58	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.2 - Haematology - At the end of recovery - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
PLATELETS 10^9/l	894.2	46.1	5	872.8	94.1	5
PROTHROMBIN TIME sec	16.98	0.45	5	16.38	0.40	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 5.2 - Haematology - At the end of recovery - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
WHITE BLOOD CELL COUNT 10^9/l	8.656	1.684	5	7.730	0.738	5
NEUTROPHILS %	8.60	1.02	5	7.84	2.56	5
LYMPHOCYTES %	84.44	0.42	5	86.94	2.46	5
MONOCYTES %	3.98	0.68	5	3.00*	0.46	5
EOSINOPHILS %	1.60	0.48	5	1.04	0.27	5
BASOPHILS %	0.20	0.07	5	0.14	0.05	5
LARGE UNSTAINED CELLS %	1.20	0.19	5	1.06	0.48	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett's test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.1 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
ALKALINE PHOSPHATASE U/l		257.92	40.78	5	240.86	15.84	5	303.28	34.38	5	341.82*	61.48	5
ALANINE AMINO-TRANSFERASE U/l	($)	31.56	2.81	5	33.94	7.70	5	129.20	103.26	5	100.62**	33.16	5
ASPARTATE AMINO-TRANSFERASE U/l	($)	81.10	8.16	5	75.28	7.77	5	127.90	49.84	5	130.30*	33.95	5
GAMMA-GLUTAMYL TRANSFERASE U/l	($)	0.220	0.164	5	0.200	0.308	5	0.020	0.045	5	0.060	0.055	5
TOTAL BILIRUBIN mg/dl		0.112	0.015	5	0.074	0.032	5	0.076	0.022	5	0.190**	0.041	5
TOTAL CHOLESTEROL mg/dl		74.32	11.92	5	49.16**	9.84	5	57.02*	7.18	5	78.52	7.62	5
TRIGLYCERIDES mg/dl	($)	37.86	9.19	5	27.18	7.78	5	18.50**	1.61	5	36.24	2.37	5
GLUCOSE mg/dl		106.58	14.32	5	121.18	18.14	5	119.38	8.92	5	124.20	7.26	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett's test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.1 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
UREA mg/dl		45.48	6.14	5	47.68	3.35	5	52.62	4.98	5	67.46**	3.42	5
CREATININE mg/dl		0.336	0.053	5	0.322	0.028	5	0.316	0.037	5	0.298	0.026	5
CHLORIDE mmol/l		92.90	1.00	5	93.60	1.05	5	93.56	0.83	5	94.94**	0.72	5
INORGANIC PHOSPHORUS mg/dl		8.54	0.33	5	8.56	0.34	5	7.78*	0.27	5	6.68**	0.50	5
CALCIUM mmol/l	($)	2.624	0.077	5	2.636	0.060	5	2.612	0.033	5	2.312	0.337	5
SODIUM mmol/l		144.18	0.54	5	143.00	1.88	5	150.26**	1.25	5	146.10	0.86	5
POTASSIUM mmol/l	($)	3.874	0.161	5	3.720	0.072	5	3.996	0.117	5	4.488	0.592	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett's test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.1 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
TOTAL PROTEIN g/dl	($)	6.46	0.18	5	5.90**	0.19	5	6.16	0.17	5	5.40*	0.60	5
ALBUMIN g/dl		4.00	0.07	5	3.78	0.08	5	3.98	0.15	5	3.50**	0.27	5
GLOBULIN g/dl	($)	2.46	0.11	5	2.12*	0.15	5	2.18	0.20	5	1.90	0.49	5
ALBUMIN/GLOBULIN RATIO	($)	1.63	0.05	5	1.79	0.12	5	1.84	0.21	5	1.93	0.43	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.1 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units		Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
ALKALINE PHOSPHATASE U/l		207.84	29.86	5	175.63	25.89	4	237.76	25.24	5	220.30	50.65	5
ALANINE AMINO-TRANSFERASE U/l	($)	31.14	3.00	5	28.03	3.16	4	44.64	13.94	5	38.86	12.16	5
ASPARTATE AMINO-TRANSFERASE U/l		80.88	14.22	5	73.05	9.34	4	84.20	11.29	5	82.30	12.41	5
GAMMA-GLUTAMYL TRANSFERASE U/l	($)	1.320	1.724	5	1.475	0.330	4	0.800	0.300	5	2.340	2.362	5
TOTAL BILIRUBIN mg/dl		0.090	0.017	5	0.063	0.010	4	0.036**	0.015	5	0.060*	0.023	5
TOTAL CHOLESTEROL mg/dl		80.54	12.00	5	70.58	8.98	4	71.34	10.23	5	75.46	12.16	5
TRIGLYCERIDES mg/dl		31.30	7.08	5	26.10	8.46	4	27.72	4.06	5	30.60	6.84	5
GLUCOSE mg/dl		111.58	7.99	5	105.65	14.48	4	117.06	10.03	5	133.80**	6.47	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.1 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
UREA mg/dl	48.90	5.99	5	47.38	2.17	4	49.30	6.86	5	60.84*	9.13	5
CREATININE mg/dl	0.446	0.042	5	0.410	0.050	4	0.424	0.024	5	0.380*	0.035	5
CHLORIDE mmol/l	94.34	0.96	5	95.58	1.19	4	96.54*	1.31	5	96.00	1.03	5
INORGANIC PHOSPHORUS mg/dl	7.47	0.37	5	7.51	0.36	4	6.97	0.37	5	6.79*	0.42	5
CALCIUM mmol/l	2.614	0.032	5	2.705	0.054	4	2.590	0.137	5	2.664	0.092	5
SODIUM mmol/l	143.94	0.59	5	143.45	0.91	4	145.66	0.75	5	143.68	1.67	5
POTASSIUM mmol/l	3.700	0.454	5	3.605	0.131	4	3.434	0.304	5	3.552	0.296	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.1 - Clinical chemistry - At the end of treatment - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
TOTAL PROTEIN g/dl	6.26	0.21	5	6.40	0.27	4	6.60	0.16	5	6.26	0.23	5
ALBUMIN g/dl	4.16	0.15	5	4.18	0.21	4	4.40	0.16	5	4.38	0.18	5
GLOBULIN g/dl	2.10	0.23	5	2.23	0.17	4	2.20	0.12	5	1.88	0.13	5
ALBUMIN/GLOBULIN RATIO	2.00	0.25	5	1.89	0.18	4	2.01	0.16	5	2.34*	0.18	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.2 - Clinical chemistry - At the end of recovery - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
ALKALINE PHOSPHATASE U/l	216.20	21.08	5	305.44**	33.60	5
ALANINE AMINO-TRANSFERASE U/l	31.98	1.84	5	35.18	10.68	5
ASPARTATE AMINO-TRANSFERASE U/l	61.48	1.95	5	60.84	8.69	5
GAMMA-GLUTAMYL TRANSFERASE U/l	1.120	0.936	5	0.960	0.472	5
TOTAL BILIRUBIN mg/dl	0.128	0.026	5	0.198	0.091	5
TOTAL CHOLESTEROL mg/dl	75.56	7.98	5	132.76**	22.36	5
TRIGLYCERIDES mg/dl	42.64	4.75	5	23.54**	5.64	5
GLUCOSE mg/dl	119.62	4.00	5	144.10	23.60	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.2 - Clinical chemistry - At the end of recovery - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
UREA mg/dl	44.52	6.76	5	60.12**	7.29	5
CREATININE mg/dl	0.348	0.037	5	0.230**	0.024	5
CHLORIDE mmol/l	92.92	0.68	5	94.24	1.44	5
INORGANIC PHOSPHORUS mg/dl	8.12	0.18	5	7.00	1.09	5
CALCIUM mmol/l	2.686	0.115	5	2.548	0.225	5
SODIUM mmol/l	147.22	0.53	5	144.14**	1.55	5
POTASSIUM mmol/l	4.278	0.249	5	4.490	0.740	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.2 - Clinical chemistry - At the end of recovery - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
TOTAL PROTEIN g/dl	6.46	0.09	5	5.74*	0.51	5
ALBUMIN g/dl	3.88	0.11	5	3.84	0.35	5
GLOBULIN g/dl	2.58	0.18	5	1.90**	0.19	5
ALBUMIN/GLOBULIN RATIO	1.51	0.13	5	2.02**	0.12	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett's test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.2 - Clinical chemistry - At the end of recovery - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
ALKALINE PHOSPHATASE U/l	164.40	14.39	5	140.74	23.33	5
ALANINE AMINO-TRANSFERASE U/l	26.48	2.80	5	28.76	4.51	5
ASPARTATE AMINO-TRANSFERASE U/l	76.22	5.99	5	54.30**	1.46	5
GAMMA-GLUTAMYL TRANSFERASE U/l	1.260	0.716	5	0.920	0.729	5
TOTAL BILIRUBIN mg/dl	0.164	0.009	5	0.104**	0.015	5
TOTAL CHOLESTEROL mg/dl	70.06	15.54	5	78.08	3.46	5
TRIGLYCERIDES mg/dl	43.54	5.36	5	31.58**	4.86	5
GLUCOSE mg/dl	103.74	6.41	5	135.78*	22.68	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.2 - Clinical chemistry - At the end of recovery - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
UREA mg/dl	67.82	7.50	5	61.06	9.77	5
CREATININE mg/dl	0.552	0.067	5	0.358**	0.041	5
CHLORIDE mmol/l	95.00	0.48	5	93.88*	0.91	5
INORGANIC PHOSPHORUS mg/dl	7.32	0.32	5	6.80*	0.18	5
CALCIUM mmol/l	2.690	0.053	5	2.734	0.154	5
SODIUM mmol/l	147.92	0.51	5	145.48**	0.62	5
POTASSIUM mmol/l	3.322	0.240	5	3.722*	0.220	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 6.2 - Clinical chemistry - At the end of recovery - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
TOTAL PROTEIN g/dl	6.20	0.25	5	6.40	0.36	5
ALBUMIN g/dl	4.12	0.15	5	4.50*	0.32	5
GLOBULIN g/dl	2.08	0.19	5	1.90	0.16	5
ALBUMIN/GLOBULIN RATIO	1.99	0.20	5	2.38*	0.25	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 7.1 - Urinalysis - At the end of treatment - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
URINE VOLUME (OVERNIGHT) ml	5.80	0.57	5	6.60	0.96	5	6.80	1.35	5	7.00	0.79	5
SPECIFIC GRAVITY	1.0180	0.0045	5	1.0230	0.0045	5	1.0120	0.0057	5	1.0150	0.0035	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 7.1 - Urinalysis - At the end of treatment - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units	Control Mean	SD	n	Group 2 Mean	SD	n	Group 3 Mean	SD	n	Group 4 Mean	SD	n
URINE VOLUME (OVERNIGHT) ml	6.30	0.91	5	7.25	1.94	4	4.80	1.82	5	4.20	1.79	5
SPECIFIC GRAVITY	1.0150	0.0035	5	1.0175	0.0029	4	1.0220	0.0057	5	1.0270**	0.0067	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 7.2 - Urinalysis - At the end of recovery - Group mean data

STUDY NO.: [redacted]

MALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
URINE VOLUME (OVERNIGHT) ml	8.60	3.49	5	7.10	3.17	5
SPECIFIC GRAVITY	1.0090	0.0022	5	1.0190*	0.0065	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 7.2 - Urinalysis - At the end of recovery - Group mean data

STUDY NO.: [redacted]

FEMALES

Parameter/units	Control Mean	SD	n	Group 4 Mean	SD	n
URINE VOLUME (OVERNIGHT) ml	3.40	1.67	5	5.50	2.24	5
SPECIFIC GRAVITY	1.0210	0.0074	5	1.0270	0.0045	5

Controls from group(s): 1 Subgroup(s): 1
* = mean value of group is significantly different from control at p < 0.05
** = mean value of group is significantly different from control at p < 0.01
Statistical analysis: Dunnett`s test if group variances are homogeneous
Modified t test if group variances are inhomogeneous ($)
Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 8.1 - Terminal body weight (g) - Final sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Controls from group(s): 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	346.94	333.88	341.18	277.10
Standard deviation	9.70	14.30	10.75	24.25
Group diff. at p < 0.05		25.95	25.95	25.95*
Group diff. at p < 0.01		33.94	33.94	33.94*

Analysis of variance: F ratio = 20.73 Df = 3/ 16 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 8.1 - Terminal body weight (g) - Final sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Controls from group(s): 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	221.56	221.05	212.82	196.14
Standard deviation	10.62	8.38	11.21	8.83
Group diff. at p < 0.05		17.37	16.38	16.38*
Group diff. at p < 0.01		22.81	21.51	21.51*

Analysis of variance: F ratio = 6.91 Df = 3/ 15 F probability = 0.004
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 8.2 - Terminal body weight (g) - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Controls from group(s): 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	364.66	273.60
Standard deviation	18.41	31.02
Group diff. at p < 0.05		37.32*
Group diff. at p < 0.01		54.31*

Analysis of variance: F ratio = 31.86 Df = 1/ 8 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 8.2 - Terminal body weight (g) - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Controls from group(s): 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	222.52	202.66
Standard deviation	6.83	8.92
Group diff. at p < 0.05		11.62*
Group diff. at p < 0.01		16.92*

Analysis of variance: F ratio = 15.62 Df = 1/ 8 F probability = 0.004
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Adrenals Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.0486	0.0498	0.0500	0.0428
Standard deviation	0.0099	0.0029	0.0125	0.0035
Group diff. at p < 0.05		0.0128	0.0198	0.0130
Group diff. at p < 0.01		0.0213	0.0330	0.0217

Analysis of variance: F ratio = 0.84 Df = 3/ 16 F probability = 0.495
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Brain Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	1.806	1.806	1.824	1.761
Standard deviation	0.050	0.054	0.023	0.085
Group diff. at p < 0.05		0.094	0.094	0.094
Group diff. at p < 0.01		0.123	0.123	0.123

Analysis of variance: F ratio = 1.10 Df = 3/ 16 F probability = 0.380
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Epididymides Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	1.0898	1.1072	1.0976	1.0682
Standard deviation	0.0381	0.0851	0.0871	0.0598
Group diff. at p < 0.05		0.1155	0.1155	0.1155
Group diff. at p < 0.01		0.1510	0.1510	0.1510

Analysis of variance: F ratio = 0.28 Df = 3/ 16 F probability = 0.841
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Heart Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	1.234	1.168	1.233	0.917
Standard deviation	0.080	0.070	0.068	0.096
Group diff. at p < 0.05		0.130	0.130	0.130*
Group diff. at p < 0.01		0.170	0.170	0.170*

Analysis of variance: F ratio = 18.10 Df = 3/ 16 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Kidneys Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	2.145	2.140	2.358	2.087
Standard deviation	0.087	0.091	0.173	0.220
Group diff. at p < 0.05		0.251	0.251	0.251
Group diff. at p < 0.01		0.329	0.329	0.329

Analysis of variance: F ratio = 3.06 Df = 3/ 16 F probability = 0.058
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Liver Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	9.251	10.462	14.270	16.995
Standard deviation	0.638	0.799	0.837	1.345
Group diff. at p < 0.05		1.546	1.546*	1.546*
Group diff. at p < 0.01		2.021	2.021*	2.021*

Analysis of variance: F ratio = 70.90 Df = 3/ 16 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Spleen Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.8874	0.8012	0.8090	0.5482
Standard deviation	0.0717	0.1129	0.1089	0.1099
Group diff. at p < 0.05		0.1677	0.1677	0.1677*
Group diff. at p < 0.01		0.2193	0.2193	0.2193*

Analysis of variance: F ratio = 10.39 Df = 3/ 16 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Testes Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	3.7378	3.7782	3.7664	3.6210
Standard deviation	0.2163	0.1372	0.2113	0.1819
Group diff. at p < 0.05		0.3103	0.3103	0.3103
Group diff. at p < 0.01		0.4059	0.4059	0.4059

Analysis of variance: F ratio = 0.72 Df = 3/ 16 F probability = 0.556
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Thymus Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.5252	0.5508	0.5460	0.3096
Standard deviation	0.0645	0.1063	0.0619	0.1004
Group diff. at p < 0.05		0.1405	0.1405	0.1405*
Group diff. at p < 0.01		0.1837	0.1837	0.1837*

Analysis of variance: F ratio = 9.17 Df = 3/ 16 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Thyroid Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.0250	0.0258	0.0268	0.0252
Standard deviation	0.0025	0.0029	0.0004	0.0024
Group diff. at p < 0.05		0.0048	0.0032	0.0043
Group diff. at p < 0.01		0.0081	0.0054	0.0072

Analysis of variance: F ratio = 0.62 Df = 3/ 16 F probability = 0.616
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Adrenals Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.0648	0.0590	0.0672	0.0550
Standard deviation	0.0013	0.0036	0.0112	0.0082
Group diff. at p < 0.05		0.0059	0.0140	0.0103
Group diff. at p < 0.01		0.0108	0.0233	0.0171

Analysis of variance: F ratio = 2.80 Df = 3/ 15 F probability = 0.075
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Brain Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	1.669	1.642	1.679	1.620
Standard deviation	0.064	0.037	0.042	0.062
Group diff. at p < 0.05		0.094	0.088	0.088
Group diff. at p < 0.01		0.123	0.116	0.116

Analysis of variance: F ratio = 1.25 Df = 3/ 15 F probability = 0.328
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Heart Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.858	0.832	0.835	0.759
Standard deviation	0.076	0.107	0.032	0.102
Group diff. at p < 0.05		0.145	0.137	0.137
Group diff. at p < 0.01		0.190	0.179	0.179

Analysis of variance: F ratio = 1.34 Df = 3/ 15 F probability = 0.299
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Kidneys Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	1.414	1.377	1.432	1.416
Standard deviation	0.112	0.116	0.058	0.097
Group diff. at p < 0.05		0.170	0.161	0.161
Group diff. at p < 0.01		0.224	0.211	0.211

Analysis of variance: F ratio = 0.25 Df = 3/ 15 F probability = 0.860
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Liver Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	5.865	5.942	6.518	8.540
Standard deviation	0.407	0.410	0.359	0.438
Group diff. at p < 0.05		0.708	0.667	0.667*
Group diff. at p < 0.01		0.929	0.876	0.876*

Analysis of variance: F ratio = 46.60 Df = 3/ 15 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Ovaries Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.1274	0.1140	0.1186	0.1168
Standard deviation	0.0153	0.0181	0.0159	0.0110
Group diff. at p < 0.05		0.0265	0.0249	0.0249
Group diff. at p < 0.01		0.0347	0.0328	0.0328

Analysis of variance: F ratio = 0.69 Df = 3/ 15 F probability = 0.574
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Spleen Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.6978	0.6058	0.5358	0.4474
Standard deviation	0.0848	0.1240	0.0461	0.0487
Group diff. at p < 0.05		0.1378	0.1299*	0.1299*
Group diff. at p < 0.01		0.1809	0.1706	0.1706*

Analysis of variance: F ratio = 9.03 Df = 3/ 15 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Thymus Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.3754	0.3908	0.4076	0.3210
Standard deviation	0.0511	0.0663	0.0643	0.0215
Group diff. at p < 0.05		0.0927	0.0874	0.0874
Group diff. at p < 0.01		0.1217	0.1147	0.1147

Analysis of variance: F ratio = 2.47 Df = 3/ 15 F probability = 0.101
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.1 - Absolute organ weights (g) - Final sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Thyroid Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.0146	0.0160	0.0148	0.0148
Standard deviation	0.0029	0.0018	0.0019	0.0013
Group diff. at p < 0.05		0.0036	0.0034	0.0034
Group diff. at p < 0.01		0.0048	0.0045	0.0045

Analysis of variance: F ratio = 0.40 Df = 3/ 15 F probability = 0.757
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Adrenals Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.0494	0.0456
Standard deviation	0.0095	0.0101
Group diff. at p < 0.05		0.0144
Group diff. at p < 0.01		0.0209

Analysis of variance: F ratio = 0.37 Df = 1/ 8 F probability = 0.563
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Brain Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	1.773	1.661
Standard deviation	0.045	0.077
Group diff. at p < 0.05		0.093*
Group diff. at p < 0.01		0.135

Analysis of variance: F ratio = 7.77 Df = 1/ 8 F probability = 0.023
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Epididymides Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	1.1990	0.9824
Standard deviation	0.1162	0.1777
Group diff. at p < 0.05		0.2197
Group diff. at p < 0.01		0.3197

Analysis of variance: F ratio = 5.20 Df = 1/ 8 F probability = 0.050
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Heart Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	1.217	0.897
Standard deviation	0.048	0.139
Group diff. at p < 0.05		0.152*
Group diff. at p < 0.01		0.222*

Analysis of variance: F ratio = 23.63 Df = 1/ 8 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Kidneys Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	2.152	2.089
Standard deviation	0.178	0.295
Group diff. at p < 0.05		0.357
Group diff. at p < 0.01		0.519

Analysis of variance: F ratio = 0.17 Df = 1/ 8 F probability = 0.694
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Liver Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	9.188	17.336
Standard deviation	0.931	1.733
Group diff. at p < 0.05		2.035*
Group diff. at p < 0.01		2.962*

Analysis of variance: F ratio = 85.76 Df = 1/ 8 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Spleen Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.8638	0.5860
Standard deviation	0.1165	0.0570
Group diff. at p < 0.05		0.1342*
Group diff. at p < 0.01		0.1953*

Analysis of variance: F ratio = 22.94 Df = 1/ 8 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Testes Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	3.7084	3.4254
Standard deviation	0.1403	0.3016
Group diff. at p < 0.05		0.3441
Group diff. at p < 0.01		0.5008

Analysis of variance: F ratio = 3.62 Df = 1/ 8 F probability = 0.091
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Thymus Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.4750	0.3146
Standard deviation	0.0472	0.1459
Group diff. at p < 0.05		0.1586*
Group diff. at p < 0.01		0.2308

Analysis of variance: F ratio = 5.47 Df = 1/ 8 F probability = 0.046
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Thyroid Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.0198	0.0220
Standard deviation	0.0033	0.0060
Group diff. at p < 0.05		0.0071
Group diff. at p < 0.01		0.0103

Analysis of variance: F ratio = 0.52 Df = 1/ 8 F probability = 0.497
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Adrenals Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.0552	0.0516
Standard deviation	0.0090	0.0047
Group diff. at p < 0.05		0.0105
Group diff. at p < 0.01		0.0154

Analysis of variance: F ratio = 0.62 Df = 1/ 8 F probability = 0.457
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Brain Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	1.660	1.642
Standard deviation	0.074	0.059
Group diff. at p < 0.05		0.098
Group diff. at p < 0.01		0.143

Analysis of variance: F ratio = 0.18 Df = 1/ 8 F probability = 0.687
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Heart Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.808	0.734
Standard deviation	0.037	0.032
Group diff. at p < 0.05		0.050*
Group diff. at p < 0.01		0.073*

Analysis of variance: F ratio = 11.55 Df = 1/ 8 F probability = 0.009
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Kidneys Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	1.359	1.399
Standard deviation	0.034	0.082
Group diff. at p < 0.05		0.092
Group diff. at p < 0.01		0.134

Analysis of variance: F ratio = 0.98 Df = 1/ 8 F probability = 0.353
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Liver Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	5.413	8.420
Standard deviation	0.167	0.144
Group diff. at p < 0.05		0.228*
Group diff. at p < 0.01		0.332*

Analysis of variance: F ratio = 929.52 Df = 1/ 8 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Ovaries Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.1162	0.1046
Standard deviation	0.0063	0.0158
Group diff. at p < 0.05		0.0176
Group diff. at p < 0.01		0.0256

Analysis of variance: F ratio = 2.32 Df = 1/ 8 F probability = 0.164
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Spleen Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.6078	0.5278
Standard deviation	0.0684	0.0244
Group diff. at p < 0.05		0.0751*
Group diff. at p < 0.01		0.1093

Analysis of variance: F ratio = 6.08 Df = 1/ 8 F probability = 0.038
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Thymus Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.3898	0.3382
Standard deviation	0.1270	0.0443
Group diff. at p < 0.05		0.1392
Group diff. at p < 0.01		0.2025

Analysis of variance: F ratio = 0.74 Df = 1/ 8 F probability = 0.420
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 9.2 - Absolute organ weights (g) - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Thyroid Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.0182	0.0196
Standard deviation	0.0054	0.0050
Group diff. at p < 0.05		0.0076
Group diff. at p < 0.01		0.0111

Analysis of variance: F ratio = 0.18 Df = 1/ 8 F probability = 0.683
Note: a * indicates group mean is significantly different from control at level of significance shown.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Adrenals Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.0140	0.0149	0.0146	0.0155
Standard deviation	0.0029	0.0011	0.0033	0.0008
Group diff. at p < 0.05		0.0039	0.0055	0.0038
Group diff. at p < 0.01		0.0065	0.0091	0.0063

Analysis of variance: F ratio = 0.34 Df = 3/ 16 F probability = 0.797
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Brain Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.521	0.541	0.535	0.640
Standard deviation	0.022	0.009	0.015	0.071
Group diff. at p < 0.05		0.030	0.034	0.092*
Group diff. at p < 0.01		0.050	0.056	0.154

Analysis of variance: F ratio = 10.22 Df = 3/ 16 F probability = 0.001
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Epididymides Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.3144	0.3318	0.3216	0.3890
Standard deviation	0.0154	0.0235	0.0211	0.0538
Group diff. at p < 0.05		0.0526	0.0526	0.0526*
Group diff. at p < 0.01		0.0688	0.0688	0.0688*

Analysis of variance: F ratio = 5.60 Df = 3/ 16 F probability = 0.008
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Heart Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.356	0.350	0.362	0.331
Standard deviation	0.028	0.022	0.018	0.022
Group diff. at p < 0.05		0.037	0.037	0.037
Group diff. at p < 0.01		0.049	0.049	0.049

Analysis of variance: F ratio = 1.70 Df = 3/ 16 F probability = 0.206
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Kidneys Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.618	0.641	0.691	0.753
Standard deviation	0.016	0.023	0.034	0.051
Group diff. at p < 0.05		0.055	0.055*	0.055*
Group diff. at p < 0.01		0.072	0.072*	0.072*

Analysis of variance: F ratio = 15.81 Df = 3/ 16 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Liver Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	2.665	3.130	4.182	6.138
Standard deviation	0.132	0.109	0.194	0.141
Group diff. at p < 0.05		0.242*	0.242*	0.242*
Group diff. at p < 0.01		0.316*	0.316*	0.316*

Analysis of variance: F ratio = 546.08 Df = 3/ 16 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Spleen Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.2559	0.2392	0.2367	0.1968
Standard deviation	0.0214	0.0246	0.0258	0.0269
Group diff. at p < 0.05		0.0406	0.0406	0.0406*
Group diff. at p < 0.01		0.0531	0.0531	0.0531*

Analysis of variance: F ratio = 5.12 Df = 3/ 16 F probability = 0.011
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Testes Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	1.0790	1.1324	1.1047	1.3140
Standard deviation	0.0864	0.0382	0.0695	0.1273
Group diff. at p < 0.05		0.1419	0.1419	0.1419*
Group diff. at p < 0.01		0.1856	0.1856	0.1856*

Analysis of variance: F ratio = 7.58 Df = 3/ 16 F probability = 0.002
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Thymus Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.1515	0.1649	0.1599	0.1102
Standard deviation	0.0193	0.0303	0.0156	0.0289
Group diff. at p < 0.05		0.0399	0.0399	0.0399*
Group diff. at p < 0.01		0.0522	0.0522	0.0522

Analysis of variance: F ratio = 5.24 Df = 3/ 16 F probability = 0.010
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Thyroid Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	2	3	4
Number/group	5	5	5	5
Mean	0.0072	0.0078	0.0079	0.0091
Standard deviation	0.0009	0.0011	0.0002	0.0006
Group diff. at p < 0.05		0.0018	0.0011	0.0013*
Group diff. at p < 0.01		0.0030	0.0019	0.0022

Analysis of variance: F ratio = 5.16 Df = 3/ 16 F probability = 0.011
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Adrenals Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.0293	0.0267	0.0317	0.0280
Standard deviation	0.0012	0.0009	0.0058	0.0039
Group diff. at p < 0.05		0.0021*	0.0074	0.0051
Group diff. at p < 0.01		0.0036	0.0124	0.0085

Analysis of variance: F ratio = 1.54 Df = 3/ 15 F probability = 0.244
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Brain Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.755	0.744	0.791	0.826
Standard deviation	0.053	0.044	0.051	0.013
Group diff. at p < 0.05		0.076	0.071	0.071
Group diff. at p < 0.01		0.099	0.094	0.094

Analysis of variance: F ratio = 3.50 Df = 3/ 15 F probability = 0.042
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Heart Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.388	0.376	0.394	0.386
Standard deviation	0.037	0.037	0.033	0.038
Group diff. at p < 0.05		0.063	0.060	0.060
Group diff. at p < 0.01		0.083	0.078	0.078

Analysis of variance: F ratio = 0.19 Df = 3/ 15 F probability = 0.899
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Kidneys Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.638	0.622	0.673	0.723
Standard deviation	0.040	0.040	0.009	0.062
Group diff. at p < 0.05		0.081	0.051	0.092
Group diff. at p < 0.01		0.143	0.086	0.153

Analysis of variance: F ratio = 5.21 Df = 3/ 15 F probability = 0.012
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Liver Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	2.646	2.686	3.065	4.360
Standard deviation	0.097	0.088	0.143	0.275
Group diff. at p < 0.05		0.301	0.284*	0.284*
Group diff. at p < 0.01		0.396	0.373*	0.373*

Analysis of variance: F ratio = 105.90 Df = 3/ 15 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Ovaries Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.0574	0.0515	0.0560	0.0596
Standard deviation	0.0049	0.0072	0.0091	0.0062
Group diff. at p < 0.05		0.0123	0.0116	0.0116
Group diff. at p < 0.01		0.0161	0.0152	0.0152

Analysis of variance: F ratio = 1.05 Df = 3/ 15 F probability = 0.401
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Spleen Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.3158	0.2729	0.2523	0.2278
Standard deviation	0.0431	0.0467	0.0259	0.0178
Group diff. at p < 0.05		0.0605	0.0571*	0.0571*
Group diff. at p < 0.01		0.0795	0.0749	0.0749*

Analysis of variance: F ratio = 5.80 Df = 3/ 15 F probability = 0.008
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Thymus Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.1690	0.1776	0.1923	0.1641
Standard deviation	0.0166	0.0354	0.0357	0.0160
Group diff. at p < 0.05		0.0474	0.0447	0.0447
Group diff. at p < 0.01		0.0622	0.0587	0.0587

Analysis of variance: F ratio = 1.04 Df = 3/ 15 F probability = 0.403
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.1 - Relative organ weights° - Final sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Thyroid Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	2	3	4
Number/group	5	4	5	5
Mean	0.0066	0.0072	0.0070	0.0076
Standard deviation	0.0013	0.0008	0.0010	0.0008
Group diff. at p < 0.05		0.0018	0.0017	0.0017
Group diff. at p < 0.01		0.0024	0.0022	0.0022

Analysis of variance: F ratio = 0.78 Df = 3/ 15 F probability = 0.525
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Adrenals Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.0135	0.0166
Standard deviation	0.0022	0.0031
Group diff. at p < 0.05		0.0039
Group diff. at p < 0.01		0.0057

Analysis of variance: F ratio = 3.39 Df = 1/ 8 F probability = 0.101
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Brain Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.487	0.613
Standard deviation	0.027	0.068
Group diff. at p < 0.05		0.076*
Group diff. at p < 0.01		0.111*

Analysis of variance: F ratio = 14.68 Df = 1/ 8 F probability = 0.005
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Epididymides Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.3287	0.3584
Standard deviation	0.0245	0.0527
Group diff. at p < 0.05		0.0601
Group diff. at p < 0.01		0.0874

Analysis of variance: F ratio = 1.31 Df = 1/ 8 F probability = 0.286
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Heart Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.334	0.326
Standard deviation	0.013	0.015
Group diff. at p < 0.05		0.021
Group diff. at p < 0.01		0.030

Analysis of variance: F ratio = 0.73 Df = 1/ 8 F probability = 0.421
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Kidneys Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.590	0.762
Standard deviation	0.023	0.047
Group diff. at p < 0.05		0.054*
Group diff. at p < 0.01		0.078*

Analysis of variance: F ratio = 55.33 Df = 1/ 8 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Liver Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	2.515	6.348
Standard deviation	0.148	0.248
Group diff. at p < 0.05		0.299*
Group diff. at p < 0.01		0.435*

Analysis of variance: F ratio = 878.42 Df = 1/ 8 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Spleen Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.2363	0.2148
Standard deviation	0.0228	0.0119
Group diff. at p < 0.05		0.0266
Group diff. at p < 0.01		0.0387

Analysis of variance: F ratio = 3.50 Df = 1/ 8 F probability = 0.096
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Testes Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	1.0199	1.2583
Standard deviation	0.0815	0.1112
Group diff. at p < 0.05		0.1426*
Group diff. at p < 0.01		0.2075*

Analysis of variance: F ratio = 14.95 Df = 1/ 8 F probability = 0.005
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

MALES

Organ: Thymus Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.1308	0.1119
Standard deviation	0.0178	0.0465
Group diff. at p < 0.05		0.0515
Group diff. at p < 0.01		0.0749

Analysis of variance: F ratio = 0.72 Df = 1/ 8 F probability = 0.425
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Thyroid Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	4
Number/group	5	5
Mean	0.0054	0.0081
Standard deviation	0.0008	0.0024
Group diff. at p < 0.05		0.0031
Group diff. at p < 0.01		0.0052

Analysis of variance: F ratio = 5.76 Df = 1/ 8 F probability = 0.042
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Adrenals Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.0248	0.0254
Standard deviation	0.0041	0.0019
Group diff. at p < 0.05		0.0046
Group diff. at p < 0.01		0.0067

Analysis of variance: F ratio = 0.10 Df = 1/ 8 F probability = 0.752
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Brain Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.746	0.812
Standard deviation	0.041	0.049
Group diff. at p < 0.05		0.066
Group diff. at p < 0.01		0.097

Analysis of variance: F ratio = 5.15 Df = 1/ 8 F probability = 0.051
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Heart Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.363	0.363
Standard deviation	0.020	0.015
Group diff. at p < 0.05		0.025
Group diff. at p < 0.01		0.037

Analysis of variance: F ratio = 0.00 Df = 1/ 8 F probability = 0.909
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Kidneys Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.611	0.691
Standard deviation	0.024	0.046
Group diff. at p < 0.05		0.054*
Group diff. at p < 0.01		0.079*

Analysis of variance: F ratio = 11.66 Df = 1/ 8 F probability = 0.009
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Liver Controls from group: 1 Data inhomogeneous by Bartlett's test (Modified t test)

Group	Control	4
Number/group	5	5
Mean	2.433	4.163
Standard deviation	0.065	0.250
Group diff. at p < 0.05		0.321*
Group diff. at p < 0.01		0.535*

Analysis of variance: F ratio = 223.95 Df = 1/ 8 F probability = 0.000
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Ovaries Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.0523	0.0516
Standard deviation	0.0032	0.0073
Group diff. at p < 0.05		0.0082
Group diff. at p < 0.01		0.0120

Analysis of variance: F ratio = 0.04 Df = 1/ 8 F probability = 0.832
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Spleen Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.2730	0.2608
Standard deviation	0.0280	0.0153
Group diff. at p < 0.05		0.0330
Group diff. at p < 0.01		0.0480

Analysis of variance: F ratio = 0.74 Df = 1/ 8 F probability = 0.419
Note: a * indicates group mean is significantly different from control at level of significance shown.

Organ: Thymus Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.1741	0.1665
Standard deviation	0.0504	0.0163
Group diff. at p < 0.05		0.0548
Group diff. at p < 0.01		0.0798

Analysis of variance: F ratio = 0.10 Df = 1/ 8 F probability = 0.751
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 10.2 - Relative organ weights° - Recovery sacrifice - Group mean data

STUDY NO.: [redacted]

FEMALES

Organ: Thyroid Controls from group: 1 Data homogeneous by Bartlett's test (Dunnett's test)

Group	Control	4
Number/group	5	5
Mean	0.0081	0.0097
Standard deviation	0.0022	0.0025
Group diff. at p < 0.05		0.0035
Group diff. at p < 0.01		0.0051

Analysis of variance: F ratio = 1.07 Df = 1/ 8 F probability = 0.333
Note: a * indicates group mean is significantly different from control at level of significance shown.
° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 11.1 - Macroscopic observations - Unscheduled deaths - Group incidence

STUDY NO.: [redacted]

	-- Females --
Group:	2
Number in group:	1
Liver	
Abnormal area(s)	1
Lungs	
Abnormal colour	1
Thymus	
Abnormal area(s)	1
Abnormal colour	1
Uterus	
Abnormal size	1
Abnormal contents	1
Abdominal cavity	
Abnormal contents	1

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 11.2 - Macroscopic observations - Final sacrifice - Group incidence

STUDY NO.: [redacted]

	-- Males --				-- Females --			
Group:	1	2	3	4	1	2	3	4
Number in group:	5	5	5	5	5	4	5	5
Adrenals								
Abnormal size	0	0	0	1	0	0	0	0
Ileum								
Abnormal contents	0	0	0	0	1	0	0	0
Jejunum								
Abnormal contents	1	0	0	0	0	0	0	0
Kidneys								
Abnormal area(s)	0	0	1	0	0	0	0	0
Abnormal colour	0	0	0	0	1	0	0	0
Liver								
Abnormal area(s)	1	0	1	2	0	0	0	0
Abnormal colour	0	0	1	3	0	0	0	1
Abnormal shape	0	0	0	2	0	0	0	0
Abnormal size	0	0	0	1	2	0	0	0
Lungs								
Abnormal area(s)	1	0	0	0	0	0	1	0
Abnormal colour	0	0	0	1	0	0	0	0
Ovaries								
Abnormal size					1	0	1	0
Seminal vesicles								
Abnormal colour	0	0	0	2				
Spleen								
Abnormal shape	0	0	1	0	1	0	1	0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 11.2 - Macroscopic observations - Final sacrifice - Group incidence

STUDY NO.: [redacted]

	-- Males --				-- Females --			
Group:	1	2	3	4	1	2	3	4
Number in group:	5	5	5	5	5	4	5	5
Stomach								
Abnormal area(s)	0	0	1	0	0	0	0	0
Abnormal size	0	0	0	1	0	0	0	0
Thymus								
Abnormal area(s)	0	1	1	0	0	0	1	0
Abnormal colour	0	0	0	0	1	0	1	0
Abnormal size	0	0	0	2	0	0	0	0
Uterus								
Abnormal size					0	0	1	0
Abnormal contents					0	0	1	0
Head								
Staining	0	0	0	0	0	0	1	0
Skin								
Staining	0	0	0	0	0	0	1	1
Tail								
Abnormal area(s)	0	1	0	0	0	0	0	0
Whole animal								
No abnormalities detected	3	3	1	0	1	4	1	3

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 11.3 - Macroscopic observations - Recovery sacrifice - Group incidence

STUDY NO.: [redacted]

	-- Males --		-- Females --	
Group:	1	4	1	4
Number in group:	5	5	5	5
Cervical nodes				
Abnormal size	1	1	0	0
Ileum				
Abnormal contents	1	0	1	0
Jejunum				
Abnormal contents	1	0	2	1
Kidneys				
Abnormal area(s)	0	2	0	0
Pelvic dilatation	0	2	0	0
Liver				
Abnormal area(s)	0	0	0	1
Abnormal colour	0	0	1	0
Abnormal shape	0	1	0	0
Abnormal size	3	2	3	0
Mesenteric nodes				
Abnormal colour	0	1	0	0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 11.3 - Macroscopic observations - Recovery sacrifice - Group incidence

STUDY NO.: [redacted]

	-- Males --		-- Females --	
Group:	1	4	1	4
Number in group:	5	5	5	5
Seminal vesicles				
Abnormal colour	0	2		
Spleen				
Abnormal shape	1	0	0	0
Stomach				
Abnormal contents	0	1	1	2
Thymus				
Abnormal area(s)	0	0	0	2
Abnormal size	0	2	0	1
Uterus				
Abnormal size			0	1
Abnormal contents			0	1
Head				
Abnormal area(s)	0	1	0	0
Staining	0	1	0	2
Skin				
Staining	0	0	2	0
Whole animal				
No abnormalities detected	2	1	1	0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 12.1 - Microscopic observations - Main phase - Group incidence

STUDY NO.: [redacted]

Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Dosage group:	Ctls	2	3	4	Ctls	2	3	4
Tissues With Diagnoses	No. in group:	5	5	5	5	5	5*	5	5
Cervical nodes	Number examined:	5	0	0	5	5	1*	0	5
REACTIVE HYPERPLASIA		0	0	0	2	0	0	0	0
Heart	Number examined:	5	0	0	5	5	1*	0	5
CHRONIC INFLAMMATION		1	0	0	0	1	0	0	0
Kidneys	Number examined:	5	0	1	5	5	1*	0	5
NEPHROPATHY		4	0	1	3	1	0	0	1
INFLAMMATORY CELL INFILTRATION		1	0	0	0	1	0	0	0
Liver	Number examined:	5	5	5	5	5	5*	5	5
INFLAMMATORY CELL FOCI		5	5	5	5	5	5*	5	5
BILE DUCT PROLIFERATION		5	5	5	5	5	4	5	5
HEPATOCYTIC HYPERTROPHY		0	4	5	5	0	0	0	5
HEPATOCYTIC NECROSIS		0	0	1	2	0	0	0	0
CHRONIC INFLAMMATION		0	0	0	1	0	0	0	0
HAEMORRHAGE		0	0	0	0	0	1*	0	0
Lungs	Number examined:	5	5	5	5	5	5*	5	5
INFLAMMATORY CELL FOCI		4	1	3	4	4	3*	4	4
AGGREGATIONS OF ALVEOLAR MACROPHAGES		0	0	0	4	0	0	0	2
PERIBRONCHIAL LYMPHOID HYPERPLASIA		2	0	0	0	0	0	0	0
VASCULAR MINERALIZATION		0	2	1	1	1	2	0	0
ALVEOLAR HAEMORRHAGE		2	0	1	1	0	1	2	2
FRAGMENT/S OF BONE		0	0	1	0	0	1*	0	0
Ovaries	Number examined:					5	1*	1	5
LUTEIN CYST						1	0	0	1
Pituitary	Number examined:	5	0	0	5	5	1*	0	5
DEVELPMENTAL CYST(S)		0	0	0	1	1	0	0	0
Prostate	Number examined:	5	0	0	5				
MIXED INFLAMMATORY CELL INFILTRATION		2	0	0	5				
Seminal vesicles	Number examined:	5	0	0	5				
COLLOID DEPLETION		0	0	0	3				

* Includes one animal which was found dead on day 23 of the study.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 12.1 - Microscopic observations - Main phase - Group incidence

STUDY NO.: [redacted]

Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --				-- Animals Affected -- Females --			
	Dosage group:	Ctls	2	3	4	Ctls	2	3	4
Tissues With Diagnoses	No. in group:	5	5	5	5	5	5*	5	5
Stomach	Number examined:	5	0	1	5	5	1*	0	5
GLANDULAR DILATATION		0	0	0	0	0	0	0	0
INFLAMMATORY CELL INFILTRATION		0	0	0	0	1	0	0	0
Thymus	Number examined:	5	5	5	5	5	5*	5	5
ATROPHY		0	0	0	3	0	0	0	1
CONGESTION/HAEMORRHAGE		0	0	0	0	0	1*	0	0
Thyroid	Number examined:	5	0	0	5	5	1*	0	5
THYRO-GLOSSAL DUCT REMNANT		1	0	0	0	0	0	0	1
Urinary bladder	Number examined:	5	0	0	5	5	1*	0	5
PROTEINACEOUS PLUG		0	0	0	2	0	0	0	0
Uterus	Number examined:					5	1*	1	5
GLANDULAR DILATATION						1	0	1	2
HYDROMETRA						0	1*	1	2
Tail	Number examined:	0	1	0	0	0	0	0	0
SCAB/S		0	1	0	0	0	0	0	0
CHRONIC INFLAMMATION		0	1	0	0	0	0	0	0

* Includes one animal which was found dead on day 23 of the study.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TABLE 12.2 - Microscopic observations - Recovery phase - Group incidence

STUDY NO.: [redacted]

Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --		-- Animals Affected -- Females --	
	Dosage group:	Ctls	4	Ctls	4
Tissues With Diagnoses	No. in group:	5	5	5	5
Liver	Number examined:	5	5	5	5
INFLAMMATORY CELL FOCI		5	5	5	5
BILE DUCT PROLIFERATION		5	5	5	5
HEPATOCYTIC HYPERTROPHY		0	5	0	5
HEPATOCYTIC NECROSIS		0	1	0	0
CHRONIC INFLAMMATION		0	0	0	0
HAEMORRHAGE		0	0	0	0
Lungs	Number examined:	5	5	5	5
INFLAMMATORY CELL FOCI		2	3	2	3
AGGREGATIONS OF ALVEOLAR MACROPHAGES		0	1	0	1
PERIBRONCHIAL LYMPHOID HYPERPLASIA		0	0	0	0
VASCULAR MINERALIZATION		3	3	1	2
ALVEOLAR HAEMORRHAGE		0	1	0	1
FRAGMENT/S OF BONE		1	0	0	0
Thymus	Number examined:	5	5	5	5
ATROPHY		0	1	0	0
CONGESTION/HAEMORRHAGE		0	0	0	0

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4-WEEK ORAL TOXICITY STUDY IN RATS
FOLLOWED BY A 2 WEEK RECOVERY PERIOD

FINAL REPORT

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Appendices

Addenda

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 1 - Mortality - Individual data

STUDY NO.: [redacted]

Animal Number	Group	Sex	Study Phase	Description of death	Date of Death	Day of Death	Terminal body Weight (g)
36710027	2	F	Dosing phase	Found dead	22.Apr.05	23	211.0

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUPI	RIGH
36710002	1	1	1	2	2	+	1
36710004		1	1	2	2	+	1
36710006		1	1	2	2	+	1
36710008		1	1	2	2	+	1
36710010		1	1	2	2	+	1
36710012		1	1	2	2	+	1
36710014		1	1	2	2	+	1
36710016		1	1	2	2	+	1
36710018		1	1	2	2	+	1
36710020		1	1	2	2	+	1
36710022	2	2	1	2	2	+	1
36710024		2	1	2	2	-	1
36710026		1	1	2	1	+	1
36710028		1	1	2	2	+	1
36710030		1	1	2	1	+	1
36710032	3	1	1	2	2	+	1
36710034		1	1	2	1	-	1
36710036		1	1	2	2	+	1
36710038		1	1	2	2	+	1
36710040		1	1	2	2	+	1
36710042	4	1	1	2	2	+	1
36710044		1	1	2	2	+	1
36710046		1	1	2	2	+	1
36710048		1	1	2	2	+	1
36710050		1	1	2	2	+	1
36710052		1	1	2	2	+	1
36710054		1	1	2	2	+	1
36710056		1	1	2	2	+	1
36710058		2	1	2	2	+	1
36710060		1	1	2	2	+	1

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		GRI1 s	GRI2 s	GRIM s	BW g	LAN1 cm	LAN2 cm	LANM cm
36710002	1		42	12	27.0	352.0	9.5	6.0	7.75
36710004			19	6	12.5	370.0	8.3	7.1	7.70
36710006			36	10	23.0	351.1	8.1	6.3	7.20
36710008			30	8	19.0	341.0	7.5	7.2	7.35
36710010			25	12	18.5	355.4	6.8	7.3	7.05
36710012			35	20	27.5	350.0	8.3	7.4	7.85
36710014			40	16	28.0	333.1	7.2	6.4	6.80
36710016			38	20	29.0	348.2	6.5	8.4	7.45
36710018			20	18	19.0	325.0	6.3	7.4	6.85
36710020			22	17	19.5	350.9	6.8	7.1	6.95
		Mean	30.7	13.9	22.30	347.67	7.53	7.06	7.295
		SD	8.7	5.0	5.45	12.36	1.01	0.69	0.385
36710022	2		10	3	6.5	357.5	5.0	4.6	4.80
36710024			29	12	20.5	331.1	8.5	7.3	7.90
36710026			26	11	18.5	335.9	10.0	8.5	9.25
36710028			10	29	19.5	353.0	7.0	4.0	5.50
36710030			11	3	7.0	363.5	5.5	5.5	5.50
		Mean	17.2	11.6	14.40	348.20	7.20	5.98	6.590
		SD	9.5	10.6	7.02	14.03	2.08	1.88	1.896
36710032	3		15	3	9.0	358.4	7.0	7.2	7.10
36710034			24	4	14.0	366.7	5.8	5.2	5.50
36710036			7	6	6.5	369.7	5.0	5.0	5.00
36710038			17	3	10.0	348.7	6.5	5.3	5.90
36710040			13	3	8.0	350.8	5.3	5.8	5.55
		Mean	15.2	3.8	9.50	358.86	5.92	5.70	5.810
		SD	6.2	1.3	2.83	9.32	0.83	0.89	0.789
36710042	4		43	6	24.5	290.4	6.5	5.0	5.75
36710044			9	7	8.0	335.1	5.8	5.3	5.55
36710046			9	2	5.5	318.0	6.5	4.2	5.35
36710048			9	3	6.0	359.3	4.5	4.5	4.50
36710050			9	4	6.5	301.9	4.0	4.0	4.00
36710052			20	3	11.5	328.7	6.2	4.6	5.40
36710054			1	2	1.5	329.7	8.5	5.8	7.15
36710056			9	3	6.0	315.8	5.0	5.2	5.10
36710058			19	6	12.5	303.5	8.0	8.5	8.25
36710060			7	6	6.5	320.0	10.0	9.5	9.75
		Mean	13.5	4.2	8.85	320.24	6.50	5.66	6.080
		SD	11.7	1.9	6.31	19.55	1.87	1.85	1.779

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUPI	RIGH
36710001	1	1	1	2	2	+	1
36710003		1	1	2	2	+	1
36710005		1	1	2	2	+	1
36710007		1	1	2	2	+	1
36710009		1	1	2	2	+	1
36710011		1	1	2	2	+	1
36710013		1	1	2	2	+	1
36710015		2	1	2	2	+	1
36710017		2	1	2	2	+	1
36710019		1	1	2	2	+	1
36710021	2	1	1	2	2	+	1
36710023		1	1	2	2	+	1
36710025		2	1	2	2	+	1
36710027		1	1	2	2	+	1
36710029		2	1	2	2	+	1
36710031	3	2	1	2	2	+	1
36710033		2	1	2	2	+	1
36710035		1	1	2	2	+	1
36710037		1	1	2	2	+	1
36710039		2	1	2	2	+	1
36710041	4	1	1	2	2	+	1
36710043		1	1	2	2	+	1
36710045		2	1	2	2	+	1
36710047		1	1	2	2	+	1
36710049		2	1	2	2	+	1
36710051		1	1	2	2	+	1
36710053		1	1	2	2	+	1
36710055		2	1	2	2	+	1
36710057		2	1	2	2	+	1
36710059		1	1	2	2	+	1

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.1 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		GRI1 s	GRI2 s	GRIM s	BW g	LAN1 cm	LAN2 cm	LANM cm
36710001	1		40	4	22.0	250.3	4.0	4.3	4.15
36710003			47	2	24.5	237.6	7.5	6.5	7.00
36710005			45	11	28.0	233.5	8.5	8.3	8.40
36710007			9	5	7.0	212.5	5.5	6.0	5.75
36710009			47	22	34.5	218.9	8.5	6.2	7.35
36710011			28	4	16.0	236.6	7.0	6.0	6.50
36710013			35	8	21.5	213.0	6.9	6.3	6.60
36710015			50	7	28.5	220.1	3.0	4.0	3.50
36710017			48	10	29.0	218.9	4.3	4.0	4.15
36710019			46	12	29.0	229.6	5.3	3.1	4.20
		Mean	39.5	8.5	24.00	227.10	6.05	5.47	5.760
		SD	12.7	5.8	7.89	12.39	1.92	1.57	1.667
36710021	2		18	16	17.0	221.3	6.2	5.4	5.80
36710023			39	20	29.5	245.9	5.3	4.8	5.05
36710025			13	22	17.5	226.5	6.0	5.5	5.75
36710027			25	18	21.5	212.5	5.9	4.8	5.35
36710029			33	19	26.0	237.0	6.8	5.9	6.35
		Mean	25.6	19.0	22.30	228.64	6.04	5.28	5.660
		SD	10.6	2.2	5.42	13.10	0.54	0.48	0.493
36710031	3		35	8	21.5	242.6	6.8	5.7	6.25
36710033			31	16	23.5	212.7	6.8	6.2	6.50
36710035			17	13	15.0	224.6	3.8	4.5	4.15
36710037			8	4	6.0	210.8	3.9	5.0	4.45
36710039			39	5	22.0	215.6	3.8	5.7	4.75
		Mean	26.0	9.2	17.60	221.26	5.02	5.42	5.220
		SD	13.0	5.2	7.26	13.05	1.63	0.67	1.079
36710041	4		22	17	19.5	199.5	4.5	3.2	3.85
36710043			11	8	9.5	208.5	4.0	5.5	4.75
36710045			4	3	3.5	220.7	6.1	3.0	4.55
36710047			40	11	25.5	230.7	7.0	6.3	6.65
36710049			33	8	20.5	213.0	4.1	3.8	3.95
36710051			15	30	22.5	218.7	6.5	5.5	6.00
36710053			13	34	23.5	194.4	6.1	7.4	6.75
36710055			19	45	32.0	209.6	7.0	6.8	6.90
36710057			11	19	15.0	213.8	2.5	3.6	3.05
36710059			6	5	5.5	206.2	4.5	3.9	4.20
		Mean	17.4	18.0	17.70	211.51	5.23	4.90	5.065
		SD	11.5	14.0	9.18	10.49	1.52	1.60	1.394

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.2 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUPI	RIGH
36710012	1	1	1	2	1	+	1
36710014		1	1	2	1	+	1
36710016		1	1	2	1	+	1
36710018		1	1	2	1	+	1
36710020		1	1	2	1	+	1
36710052	4	1	1	1	1	+	1
36710054		1	1	2	1	+	1
36710056		1	1	2	1	+	1
36710058		1	1	2	1	+	1
36710060		1	1	2	2	+	1

APPENDIX 2.2 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		GRI1 s	GRI2 s	GRIM s	BW g	LAN1 cm	LAN2 cm	LANM cm
36710012	1		3	4	3.5	395.4	4.0	5.8	4.90
36710014			3	8	5.5	368.2	8.0	9.2	8.60
36710016			24	3	13.5	392.0	7.9	5.7	6.80
36710018			5	5	5.0	362.4	5.5	7.0	6.25
36710020			4	4	4.0	392.9	7.5	7.4	7.45
		Mean	7.8	4.8	6.30	382.18	6.58	7.02	6.800
		SD	9.1	1.9	4.10	15.59	1.76	1.43	1.376
36710052	4		19	5	12.0	306.4	6.0	4.0	5.00
36710054			26	6	16.0	218.5	6.9	6.5	6.70
36710056			13	8	10.5	265.1	7.5	7.5	7.50
36710058			8	7	7.5	307.1	9.4	9.0	9.20
36710060			20	6	13.0	309.3	9.4	9.2	9.30
		Mean	17.2	6.4	11.80	281.28	7.84	7.24	7.540
		SD	6.9	1.1	3.13	39.64	1.52	2.12	1.804

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.2 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	APPR	TOUC	CLIK	TAIL	PUPI	RIGH
36710011	1	1	1	1	1	+	1
36710013		1	1	2	1	+	1
36710015		1	1	2	1	+	1
36710017		1	1	2	2	+	1
36710019		1	1	2	1	+	1
36710051	4	1	1	2	1	+	1
36710053		1	1	2	1	+	1
36710055		1	1	2	1	+	1
36710057		1	1	2	1	+	1
36710059		1	1	2	1	+	1

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 2.2 - Neurotoxicity assessment - Sensory reaction to stimuli - At the end of recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		GRI1 s	GRI2 s	GRIM s	BW g	LAN1 cm	LAN2 cm	LANM cm
36710011	1		16	3	9.5	251.6	7.5	7.7	7.60
36710013			27	10	18.5	225.1	8.1	6.5	7.30
36710015			9	9	9.0	233.6	6.1	7.2	6.65
36710017			11	10	10.5	235.4	5.1	5.9	5.50
36710019			5	5	5.0	233.4	4.5	5.5	5.00
		Mean	13.6	7.4	10.50	235.82	6.26	6.56	6.410
		SD	8.5	3.2	4.94	9.68	1.53	0.90	1.127
36710051	4		7	9	8.0	219.5	4.9	4.0	4.45
36710053			9	11	10.0	197.5	6.2	4.3	5.25
36710055			13	7	10.0	213.3	8.0	4.0	6.00
36710057			11	3	7.0	226.7	6.7	4.2	5.45
36710059			4	4	4.0	225.0	2.6	3.4	3.00
		Mean	8.8	6.8	7.80	216.40	5.68	3.98	4.830
		SD	3.5	3.3	2.49	11.79	2.05	0.35	1.164

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 3.1 - Motor activity - At the end of treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		COUN
36710002	1		673
36710004			1029
36710006			778
36710008			778
36710010			558
36710012			1048
36710014			1181
36710016			913
36710018			917
36710020			1171
		Mean	904.6
		SD	208.0
36710022	2		1162
36710024			808
36710026			786
36710028			1121
36710030			751
		Mean	925.6
		SD	198.7
36710032	3		1202
36710034			1235
36710036			1411
36710038			1179
36710040			684
		Mean	1142.2
		SD	271.9
36710042	4		384
36710044			843
36710046			1102
36710048			1176
36710050			1062
36710052			638
36710054			1286
36710056			823
36710058			812
36710060			335
		Mean	846.1
		SD	322.2

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 3.1 - Motor activity - At the end of treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		COUN
36710001	1		958
36710003			919
36710005			1183
36710007			801
36710009			1167
36710011			1108
36710013			875
36710015			1153
36710017			1181
36710019			926
		Mean	1027.1
		SD	145.6
36710021	2		894
36710023			755
36710025			1024
36710029			1018
		Mean	922.8
		SD	126.9
36710031	3		1036
36710033			875
36710035			900
36710037			1000
36710039			972
		Mean	956.6
		SD	67.5
36710041	4		838
36710043			1062
36710045			900
36710047			1169
36710049			1084
36710051			622
36710053			717
36710055			995
36710057			1049
36710059			924
		Mean	936.0
		SD	171.9

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 3.2 - Motor activity - At the end of recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		COUN
36710012	1		1109
36710014			1100
36710016			918
36710018			449
36710020			1076
		Mean	930.4
		SD	280.1
36710052	4		478
36710054			944
36710056			812
36710058			1118
36710060			969
		Mean	864.2
		SD	241.7

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 3.2 - Motor activity - At the end of recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		COUN
36710011	1		1179
36710013			813
36710015			1067
36710017			1020
36710019			820
		Mean	979.8
		SD	159.9
36710051	4		843
36710053			917
36710055			1075
36710057			844
36710059			966
		Mean	929.0
		SD	96.8

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 4.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		Day of Phase 1!	1"	8	15	22	29
36710002	1		200.5	250.1	296.2	323.2	345.0	340.0
36710004			189.6	250.6	298.6	338.3	367.8	365.3
36710006			202.4	256.0	294.8	327.6	350.8	352.5
36710008			208.0	259.0	294.7	325.9	340.6	345.0
36710010			204.6	260.6	304.0	332.2	355.1	352.6
36710012			191.2	250.5	297.2	325.0	349.5	
36710014			202.9	252.4	280.7	307.1	333.9	
36710016			198.5	250.0	285.7	318.3	347.3	
36710018			195.1	242.4	277.4	297.7	324.7	
36710020			195.4	245.2	291.6	320.5	351.0	
		(n)	10	10	10	10	10	5
		Mean	198.83	251.67	292.10	321.58	346.56	351.08
		SD	5.93	5.66	8.36	11.81	11.76	9.58
36710022	2		202.5	251.2	300.5	330.3	356.4	340.4
36710024			188.6	239.4	279.4	299.6	324.7	322.0
36710026			198.9	245.6	285.0	302.9	334.7	325.1
36710028			198.1	247.6	291.1	316.6	346.1	345.9
36710030			208.6	260.4	303.2	328.3	367.3	356.1
		(n)	5	5	5	5	5	5
		Mean	199.35	248.83	291.84	315.54	345.82	337.91
		SD	7.28	7.73	10.09	14.11	16.90	14.31

Note: ! = Pretest phase; " = Dosing phase

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 4.1 - Body weight (g) - During treatment - Individual data

STUDY NO.:[redacted]

MALES

Animal Number	Group		Day of Phase 1!	1"	8	15	22	29
36710032	3		191.5	251.5	290.5	322.5	352.8	348.6
36710034			200.0	263.1	299.5	332.4	352.3	354.5
36710036			203.3	248.6	291.2	328.3	363.9	358.5
36710038			198.4	252.0	292.7	308.6	344.5	331.6
36710040			205.3	259.3	295.5	321.6	346.1	337.9
		(n)	5	5	5	5	5	5
		Mean	199.71	254.91	293.88	322.67	351.92	346.24
		SD	5.33	6.07	3.67	9.03	7.66	11.27
36710042	4		208.7	257.4	293.9	307.7	303.0	246.5
36710044			195.4	246.5	297.2	332.3	342.8	294.7
36710046			192.3	245.0	280.9	300.0	310.9	279.5
36710048			206.9	255.6	306.9	325.5	348.5	309.1
36710050			199.8	252.7	298.6	314.7	306.9	263.7
36710052			203.2	254.1	290.5	321.5	330.0	
36710054			201.1	253.2	296.8	326.9	326.8	
36710056			202.7	255.5	293.7	316.8	313.9	
36710058			185.0	234.3	279.0	293.2	303.3	
36710060			198.2	241.6	284.9	318.1	327.6	
		(n)	10	10	10	10	10	5
		Mean	199.33	249.58	292.24	315.66	321.36	278.69
		SD	7.04	7.46	8.61	12.27	16.25	24.70

Note: ! = Pretest phase; " = Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 4.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		Day of Phase 1!	1"	8	15	22	29
36710001	1		161.4	193.7	211.4	211.6	238.3	245.9
36710003			165.9	180.7	199.3	213.1	233.4	243.7
36710005			163.7	185.7	208.7	218.7	237.6	237.3
36710007			166.7	174.9	187.6	199.5	215.0	230.1
36710009			159.8	180.3	192.7	204.4	213.1	219.0
36710011			155.0	177.5	192.4	204.6	234.8	
36710013			156.5	170.1	190.0	190.7	209.2	
36710015			153.9	159.3	171.1	188.7	207.7	
36710017			152.4	160.0	184.3	197.8	216.2	
36710019			149.8	163.3	181.2	203.3	223.9	
		(n)	10	10	10	10	10	5
		Mean	158.51	174.55	191.88	203.24	222.92	235.19
		SD	5.88	11.36	12.24	9.53	12.14	10.93
36710021	2		152.7	170.0	181.8	210.9	226.2	229.7
36710023			159.7	181.4	204.0	227.6	241.6	244.5
36710025			163.6	182.0	198.1	211.0	218.3	235.3
36710027			153.7	166.3	179.3	198.9	215.6	
36710029			168.5	184.3	196.7	218.9	223.1	238.5
		(n)	5	5	5	5	5	4
		Mean	159.66	176.80	191.97	213.44	224.97	237.02
		SD	6.66	8.07	10.83	10.67	10.19	6.18

Note: ! = Pretest phase; " = Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 4.1 - Body weight (g) - During treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		Day of Phase 1!	1"	8	15	22	29
36710031	3		166.9	180.6	218.0	227.9	234.9	253.6
36710033			162.0	181.1	196.7	205.1	223.3	226.2
36710035			154.0	163.6	189.3	199.1	220.8	234.5
36710037			157.0	169.0	187.8	193.6	205.8	222.3
36710039			151.5	172.8	182.1	198.4	213.1	221.6
		(n)	5	5	5	5	5	5
		Mean	158.28	173.42	194.78	204.80	219.57	231.64
		SD	6.18	7.53	13.99	13.53	10.97	13.29
36710041	4		151.6	169.1	164.2	189.2	195.1	210.1
36710043			156.1	167.9	191.9	194.8	212.5	209.7
36710045			157.0	175.0	184.7	202.0	209.2	203.7
36710047			166.2	170.5	194.4	206.2	225.4	219.6
36710049			169.1	189.6	199.4	214.2	222.4	222.4
36710051			162.9	181.2	196.8	205.7	224.3	
36710053			151.5	175.4	181.3	206.4	200.9	
36710055			155.8	177.7	195.4	199.4	210.1	
36710057			164.6	169.9	194.6	204.7	222.3	
36710059			154.3	185.0	194.7	202.0	211.7	
		(n)	10	10	10	10	10	5
		Mean	158.92	176.11	189.75	202.43	213.40	213.07
		SD	6.30	7.27	10.54	6.89	10.26	7.70

Note: ! = Pretest phase; " = Dosing phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 4.2 - Body weight (g) - During recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		Day of Phase 1	8	15
36710012	1		372.5	388.5	384.0
36710014			351.1	366.7	353.2
36710016			371.4	397.3	386.2
36710018			341.3	357.0	343.1
36710020			371.5	388.6	376.5
		(n)	5	5	5
		Mean	361.56	379.63	368.60
		SD	14.45	16.96	19.32
36710052	4		316.3	303.0	284.1
36710054			297.8	225.4	233.4
36710056			285.3	262.1	253.3
36710058			303.2	306.8	304.3
36710060			308.2	310.4	308.1
		(n)	5	5	5
		Mean	302.16	281.52	276.64
		SD	11.63	36.96	32.49

Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 4.2 - Body weight (g) - During recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	Day of Phase 1	8	15
36710011	1	245.3	254.0	240.8
36710013		219.9	225.9	218.1
36710015		226.3	230.3	222.7
36710017		231.9	226.4	225.6
36710019		233.3	231.9	220.8
	(n)	5	5	5
	Mean	231.34	233.68	225.59
	SD	9.42	11.63	8.92
36710051	4	206.4	220.8	201.5
36710053		203.8	202.8	194.3
36710055		206.7	215.0	200.0
36710057		220.9	224.6	214.9
36710059		201.8	226.5	213.1
	(n)	5	5	5
	Mean	207.92	217.92	204.76
	SD	7.53	9.52	8.87

Note: Data for Recovery phase

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 5.1 - Body weight change° (g) - During treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		Day of Phase 8	15	22	29
36710002	1		46.2	73.2	94.9	89.9
36710004			48.0	87.7	117.2	114.7
36710006			38.8	71.6	94.7	96.4
36710008			35.7	67.0	81.6	86.1
36710010			43.4	71.6	94.5	92.1
36710012			46.7	74.4	99.0	
36710014			28.3	54.7	81.5	
36710016			35.8	68.3	97.3	
36710018			35.0	55.3	82.3	
36710020			46.4	75.3	105.8	
		(n)	10	10	10	5
		Mean	40.42	69.91	94.89	95.83
		SD	6.66	9.66	11.31	11.20
36710022	2		49.4	79.1	105.2	89.2
36710024			40.0	60.2	85.2	82.6
36710026			39.4	57.3	89.1	79.5
36710028			43.5	69.0	98.5	98.4
36710030			42.8	68.0	106.9	95.7
		(n)	5	5	5	5
		Mean	43.01	66.71	96.99	89.07
		SD	3.97	8.55	9.59	8.14

° = body weight change relevant to Day 1 of study

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 5.1 - Body weight change° (g) - During treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		Day of Phase 8	15	22	29
36710032	3		39.1	71.0	101.3	97.2
36710034			36.4	69.3	89.2	91.4
36710036			42.6	79.7	115.3	109.9
36710038			40.8	56.6	92.5	79.7
36710040			36.1	62.2	86.8	78.6
		(n)	5	5	5	5
		Mean	38.98	67.76	97.01	91.34
		SD	2.78	8.79	11.62	13.00
36710042	4		36.5	50.3	45.6	-10.9
36710044			50.7	85.9	96.3	48.3
36710046			35.9	54.9	65.8	34.4
36710048			51.3	69.9	93.0	53.5
36710050			46.0	62.1	54.3	11.0
36710052			36.4	67.4	75.9	
36710054			43.6	73.7	73.6	
36710056			38.2	61.3	58.5	
36710058			44.7	58.9	68.9	
36710060			43.3	76.5	86.0	
		(n)	10	10	10	5
		Mean	42.66	66.08	71.78	27.26
		SD	5.78	10.74	16.62	26.92

° = body weight change relevant to Day 1 of study

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 5.1 - Body weight change° (g) - During treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	Day of Phase 8	15	22	29
36710001	1	17.8	17.9	44.6	52.2
36710003		18.6	32.4	52.7	63.0
36710005		23.0	33.0	51.8	51.6
36710007		12.7	24.6	40.1	55.2
36710009		12.4	24.1	32.8	38.7
36710011		14.9	27.1	57.3	
36710013		20.0	20.6	39.2	
36710015		11.8	29.5	48.4	
36710017		24.3	37.8	56.2	
36710019		17.9	39.9	60.5	
	(n)	10	10	10	5
	Mean	17.33	28.69	48.37	52.12
	SD	4.39	7.18	9.01	8.76
36710021	2	11.8	40.8	56.2	59.7
36710023		22.6	46.2	60.2	63.1
36710025		16.1	29.0	36.3	53.3
36710027		12.9	32.6	49.3	
36710029		12.4	34.6	38.8	54.2
	(n)	5	5	5	4
	Mean	15.17	36.64	48.17	57.59
	SD	4.48	6.86	10.46	4.66

° = body weight change relevant to Day 1 of study

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 5.1 - Body weight change° (g) - During treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		Day of Phase 8	15	22	29
36710031	3		37.5	47.3	54.3	73.0
36710033			15.5	24.0	42.2	45.1
36710035			25.7	35.4	57.2	70.8
36710037			18.8	24.6	36.8	53.3
36710039			9.4	25.6	40.3	48.8
		(n)	5	5	5	5
		Mean	21.36	31.38	46.15	58.22
		SD	10.75	10.05	9.02	12.87
36710041	4		-4.9	20.1	26.0	41.0
36710043			24.0	26.8	44.6	41.7
36710045			9.7	27.0	34.3	28.7
36710047			23.9	35.6	54.9	49.0
36710049			9.8	24.6	32.8	32.8
36710051			15.6	24.5	43.1	
36710053			5.9	31.0	25.5	
36710055			17.7	21.6	32.4	
36710057			24.8	34.8	52.5	
36710059			9.8	17.0	26.8	
		(n)	10	10	10	5
		Mean	13.63	26.32	37.29	38.67
		SD	9.45	6.11	10.84	7.99

° = body weight change relevant to Day 1 of study

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 5.2 - Body weight change° (g) - During recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	Day of Phase 1	8	15
36710012	1	122.0	137.9	133.4
36710014		98.7	114.3	100.8
36710016		121.4	147.3	136.2
36710018		98.9	114.6	100.8
36710020		126.3	143.5	131.3
	(n)	5	5	5
	Mean	113.46	131.53	120.50
	SD	13.52	15.94	18.09
36710052	4	62.2	48.9	30.0
36710054		44.6	-27.8	-19.8
36710056		29.8	6.6	-2.1
36710058		68.9	72.5	70.0
36710060		66.6	68.8	66.5
	(n)	5	5	5
	Mean	54.42	33.78	28.90
	SD	16.72	43.25	40.11

° = body weight change relevant to Day 1 of study

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 5.2 - Body weight change° (g) - During recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	Day of Phase 1	8	15
36710011	1	67.8	76.5	63.3
36710013		49.8	55.8	48.0
36710015		67.0	71.0	63.4
36710017		71.9	66.4	65.7
36710019		70.0	68.5	57.5
	(n)	5	5	5
	Mean	65.31	67.65	59.56
	SD	8.86	7.62	7.13
36710051	4	25.2	39.6	20.4
36710053		28.4	27.4	18.9
36710055		29.0	37.3	22.3
36710057		51.0	54.7	45.0
36710059		16.8	41.5	28.2
	(n)	5	5	5
	Mean	30.11	40.11	26.95
	SD	12.67	9.81	10.69

° = body weight change relevant to Day 1 of study

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Food consumption° (g/animal/day) - During treatment - Cage data

STUDY NO.: [redacted]

MALES

Cage	Group		Day of Phase 8!	8"	15	22	29
1	1		25.1	27.3	25.7	28.0	24.8
2			25.2	26.0	27.0	26.8	27.4
		(n)	2	2	2	2	2
		Mean	25.13	26.64	26.35	27.40	26.09
3	2		24.8	25.9	28.0	27.6	23.4
		(n)	1	1	1	1	1
4	3		25.2	26.6	27.6	27.7	24.0
		(n)	1	1	1	1	1
5	4		25.8	27.7	26.9	25.8	18.7
6			24.0	25.5	24.0	25.2	23.1
		(n)	2	2	2	2	2
		Mean	24.89	26.62	25.46	25.47	20.90

Note: ! = Pretest phase; " = Dosing phase
° = food consumed over the previous period

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.1 - Food consumption° (g/animal/day) - During treatment - Cage data

STUDY NO.: [redacted]

FEMALES

Cage	Group		Day of Phase 8!	8"	15	22	29
7	1		17.8	18.3	17.8	18.9	19.8
8			15.8	17.6	18.2	19.5	19.6
		(n)	2	2	2	2	2
		Mean	16.82	17.95	17.99	19.17	19.73
9	2		17.6	18.4	19.9	19.6	19.0
		(n)	1	1	1	1	1
10	3		17.5	18.5	18.5	18.9	18.5
		(n)	1	1	1	1	1
11	4		16.5	16.8	18.3	19.2	18.9
12			18.1	18.3	17.5	18.4	17.7
		(n)	2	2	2	2	2
		Mean	17.28	17.58	17.88	18.81	18.34

Note: ! = Pretest phase; " = Dosing phase
° = food consumed over the previous period

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Food consumption° (g/animal/day) - During recovery - Cage data

STUDY NO.: [redacted]

MALES

Cage	Group		Day of Phase 8	Day of Phase 14
2	1		26.8	26.8
		(n)	1	1
6	4		17.9	24.4
		(n)	1	1

Note: Data for Recovery phase
° = food consumed over the previous period

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 6.2 - Food consumption° (g/animal/day) - During recovery - Cage data

STUDY NO.: [redacted]

FEMALES

Cage	Group		Day of Phase 8	14
8	1		18.7	18.6
		(n)	1	1
12	4		19.0	18.5
		(n)	1	1

Note: Data for Recovery phase
° = food consumed over the previous period

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		RBC 10^12/l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
36710002	1		8.23	15.2	43.9	53.3	18.5	34.6
36710004	1		7.67	14.8	42.7	55.7	19.4	34.7
36710006	1		7.82	15.6	44.3	56.6	19.9	35.2
36710008	1		8.11	15.0	42.6	52.5	18.5	35.3
36710010	1		7.74	14.8	42.0	54.2	19.1	35.3
		Mean	7.914	15.08	43.10	54.46	19.08	35.02
		SD	0.243	0.33	0.96	1.69	0.60	0.34
36710022	2		7.63	15.0	42.1	55.2	19.7	35.6
36710024	2		7.71	14.9	40.9	53.1	19.4	36.5
36710026	2		7.41	14.1	39.1	52.7	19.1	36.2
36710028	2		8.15	15.1	42.4	52.0	18.5	35.6
36710030	2		8.14	15.7	44.5	54.7	19.3	35.3
		Mean	7.808	14.96	41.80	53.54	19.20	35.84
		SD	0.327	0.57	1.99	1.36	0.45	0.49
36710032	3		7.63	14.6	41.6	54.5	19.2	35.2
36710034	3		7.27	14.2	39.7	54.6	19.5	35.8
36710036	3		7.34	14.2	39.8	54.2	19.3	35.6
36710038	3		7.79	15.7	44.4	57.1	20.2	35.4
36710040	3		7.55	14.9	42.2	55.9	19.8	35.4
		Mean	7.516	14.72	41.54	55.26	19.60	35.48
		SD	0.213	0.62	1.94	1.22	0.41	0.23
36710042	4		8.68	16.4	46.6	53.7	18.9	35.2
36710044	4		7.99	15.3	43.4	54.3	19.1	35.2
36710046	4		8.44	15.9	45.1	53.5	18.8	35.2
36710048	4		7.59	14.8	42.5	56.0	19.6	34.9
36710050	4		8.26	15.7	43.6	52.8	19.1	36.1
		Mean	8.192	15.62	44.24	54.06	19.10	35.32
		SD	0.421	0.61	1.62	1.21	0.31	0.45

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		PLT 10^9/l	PT sec
36710002	1		861	15.3
36710004	1		976	15.3
36710006	1		776	16.5
36710008	1		933	15.3
36710010	1		896	16.7
		Mean	888.4	15.82
		SD	76.0	0.72
36710022	2		806	16.7
36710024	2		931	16.8
36710026	2		820	17.9
36710028	2		888	16.1
36710030	2		695	17.1
		Mean	828.0	16.92
		SD	90.1	0.66
36710032	3		848	16.5
36710034	3		723	15.6
36710036	3		771	16.6
36710038	3		760	15.8
36710040	3		683	16.1
		Mean	757.0	16.12
		SD	61.5	0.43
36710042	4		874	18.0
36710044	4		924	17.6
36710046	4		820	17.6
36710048	4		809	17.9
36710050	4		954	18.8
		Mean	876.2	17.98
		SD	63.3	0.49

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		WBC 10^9/l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
36710002	1		9.34	22.0	73.6	2.9	0.7	0.1	0.7
36710004	1		8.79	23.9	71.5	2.8	0.9	0.2	0.8
36710006	1		7.46	17.8	77.3	3.0	1.0	0.2	0.8
36710008	1		8.49	14.0	80.3	3.3	1.4	0.3	0.7
36710010	1		7.99	23.7	72.3	2.6	0.5	0.2	0.7
		Mean	8.414	20.28	75.00	2.92	0.90	0.20	0.74
		SD	0.724	4.28	3.70	0.26	0.34	0.07	0.05
36710022	2		8.96	14.5	79.3	3.5	1.3	0.2	1.2
36710024	2		10.49	7.4	85.4	4.2	1.6	0.3	1.1
36710026	2		7.23	17.8	77.4	2.8	1.0	0.1	0.9
36710028	2		7.80	11.6	81.1	4.8	1.1	0.2	1.1
36710030	2		9.41	11.0	84.2	2.7	1.3	0.2	0.5
		Mean	8.778	12.46	81.48	3.60	1.26	0.20	0.96
		SD	1.296	3.91	3.33	0.90	0.23	0.07	0.28
36710032	3		8.01	17.2	75.7	4.4	1.4	0.2	1.1
36710034	3		8.02	16.2	78.6	2.9	1.1	0.4	0.8
36710036	3		12.50	22.4	72.7	2.9	1.1	0.4	0.5
36710038	3		6.48	16.8	77.3	3.0	1.8	0.5	0.6
36710040	3		5.81	9.5	85.3	3.1	0.8	0.2	1.0
		Mean	8.164	16.42	77.92	3.26	1.24	0.34	0.80
		SD	2.609	4.59	4.68	0.64	0.38	0.13	0.25
36710042	4		6.62	17.7	74.2	6.1	0.6	0.4	1.1
36710044	4		6.50	19.8	71.7	5.1	0.9	0.9	1.6
36710046	4		7.38	5.6	89.0	3.0	1.2	0.7	0.5
36710048	4		7.63	16.9	75.4	3.2	3.0	0.6	1.0
36710050	4		5.99	12.5	81.2	4.2	0.5	0.5	1.1
		Mean	6.824	14.50	78.30	4.32	1.24	0.62	1.06
		SD	0.671	5.64	6.92	1.30	1.02	0.19	0.39

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		RBC 10^12/l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
36710001	1		6.93	13.9	38.0	54.9	20.0	36.4
36710003	1		7.07	13.7	37.2	52.7	19.4	36.8
36710005	1		6.60	13.0	35.5	53.8	19.7	36.7
36710007	1		7.44	14.4	40.2	54.0	19.3	35.8
36710009	1		6.94	13.2	36.6	52.7	19.0	36.1
		Mean	6.996	13.64	37.50	53.62	19.48	36.36
		SD	0.303	0.56	1.76	0.94	0.38	0.42
36710021	2		6.96	14.0	38.2	54.8	20.0	36.6
36710023	2		7.21	14.1	38.4	53.2	19.5	36.6
36710025	2		7.12	14.2	39.2	55.1	20.0	36.2
36710029	2		7.07	13.8	38.5	54.4	19.6	36.0
		Mean	7.090	14.03	38.58	54.38	19.78	36.35
		SD	0.104	0.17	0.43	0.83	0.26	0.30
36710031	3		7.34	14.1	38.6	52.6	19.2	36.4
36710033	3		7.10	14.1	37.8	53.3	19.8	37.2
36710035	3		6.96	13.6	37.8	54.4	19.5	35.9
36710037	3		7.02	13.8	38.1	54.3	19.6	36.1
36710039	3		7.22	14.4	39.9	55.3	20.0	36.1
		Mean	7.128	14.00	38.44	53.98	19.62	36.34
		SD	0.153	0.31	0.88	1.05	0.30	0.51
36710041	4		6.59	13.2	36.6	55.5	20.1	36.2
36710043	4		7.08	14.0	38.5	54.5	19.7	36.2
36710045	4		7.17	13.7	38.9	54.3	19.1	35.3
36710047	4		7.37	14.4	39.6	53.7	19.5	36.3
36710049	4		7.12	13.5	36.7	51.5	18.9	36.7
		Mean	7.066	13.76	38.06	53.90	19.46	36.14
		SD	0.288	0.46	1.35	1.49	0.48	0.51

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		PLT 10^9/l	PT sec
36710001	1		1057	16.7
36710003	1		840	16.8
36710005	1		940	17.2
36710007	1		NT	NT
36710009	1		135	NT
		Mean	743.0	16.90
		SD	414.9	0.26
36710021	2		1032	16.4
36710023	2		1056	17.3
36710025	2		908	16.5
36710029	2		980	17.6
		Mean	994.0	16.95
		SD	65.5	0.59
36710031	3		920	16.5
36710033	3		857	16.4
36710035	3		844	16.7
36710037	3		991	17.1
36710039	3		914	17.2
		Mean	905.2	16.78
		SD	58.6	0.36
36710041	4		843	15.5
36710043	4		840	17.4
36710045	4		832	15.9
36710047	4		743	17.2
36710049	4		853	18.0
		Mean	822.2	16.80
		SD	44.9	1.06

NT = NOT TAKEN

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.1 - Haematology - At the end of treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		WBC 10^9/l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
36710001	1		8.86	4.8	90.1	2.8	1.1	0.2	0.9
36710003	1		7.08	12.7	82.2	2.9	1.4	0.1	0.6
36710005	1		6.66	14.7	81.0	2.0	1.5	0.1	0.8
36710007	1		6.98	7.3	87.4	3.2	1.5	0.2	0.6
36710009	1		6.04	7.9	84.6	5.1	1.7	0.1	0.7
		Mean	7.124	9.48	85.06	3.20	1.44	0.14	0.72
		SD	1.052	4.09	3.73	1.15	0.22	0.05	0.13
36710021	2		7.43	17.4	74.5	5.0	2.1	0.2	0.9
36710023	2		7.59	12.3	80.9	3.8	1.8	0.1	1.0
36710025	2		6.69	11.4	83.6	2.7	1.4	0.1	0.8
36710029	2		6.99	8.8	85.0	4.0	1.2	0.2	0.8
		Mean	7.175	12.48	81.00	3.88	1.63	0.15	0.88
		SD	0.411	3.60	4.66	0.94	0.40	0.06	0.10
36710031	3		6.75	6.2	86.0	4.2	2.2	0.2	1.2
36710033	3		6.27	14.2	79.3	2.9	2.5	0.2	0.9
36710035	3		4.59	16.1	78.9	2.8	1.5	0.1	0.6
36710037	3		6.38	10.1	84.8	2.3	2.0	0.2	0.6
36710039	3		5.63	10.9	80.8	3.7	3.5	0.1	1.0
		Mean	5.924	11.50	81.96	3.18	2.34	0.16	0.86
		SD	0.848	3.84	3.25	0.76	0.74	0.05	0.26
36710041	4		3.12	9.5	86.1	2.6	1.1	0.1	0.6
36710043	4		9.47	9.2	86.3	2.6	0.9	0.1	0.9
36710045	4		5.68	11.1	83.0	3.1	1.8	0.2	0.9
36710047	4		4.06	7.2	85.9	3.8	1.9	0.2	1.0
36710049	4		6.70	7.4	86.2	3.9	1.3	0.2	1.1
		Mean	5.806	8.88	85.50	3.20	1.40	0.16	0.90
		SD	2.475	1.61	1.41	0.63	0.44	0.05	0.19

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Haematology - At the end of recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		RBC 10^12/l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
36710012	1		8.30	15.3	43.6	52.6	18.5	35.2
36710014	1		8.44	15.5	43.4	51.4	18.3	35.7
36710016	1		8.05	15.2	42.9	53.3	18.8	35.4
36710018	1		8.08	14.7	41.1	50.9	18.2	35.8
36710020	1		8.31	15.4	43.0	51.7	18.5	35.7
		Mean	8.236	15.22	42.80	51.98	18.46	35.56
		SD	0.166	0.31	0.99	0.96	0.23	0.25
36710052	4		8.05	14.7	39.4	49.0	18.3	37.4
36710054	4		6.64	12.4	33.0	49.7	18.7	37.6
36710056	4		7.62	14.3	38.9	51.0	18.8	36.8
36710058	4		7.65	14.5	39.4	51.5	19.0	36.9
36710060	4		7.55	13.9	38.8	51.5	18.4	35.8
		Mean	7.502	13.96	37.90	50.54	18.64	36.90
		SD	0.520	0.92	2.75	1.13	0.29	0.70

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Haematology - At the end of recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		PLT 10^9/l	PT sec
36710012	1		866	16.2
36710014	1		880	16.9
36710016	1		941	16.3
36710018	1		970	15.5
36710020	1		976	16.2
		Mean	926.6	16.22
		SD	50.9	0.50
36710052	4		1295	17.7
36710054	4		953	18.4
36710056	4		1247	17.0
36710058	4		877	18.0
36710060	4		1030	16.4
		Mean	1080.4	17.50
		SD	183.0	0.80

[redacted]

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Haematology - At the end of recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		WBC 10^9/l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
36710012	1		8.99	8.6	86.7	3.0	0.8	0.2	0.7
36710014	1		10.81	9.0	86.8	2.2	1.0	0.2	0.9
36710016	1		12.68	13.5	81.7	2.4	1.4	0.2	0.9
36710018	1		11.88	22.7	70.9	2.9	2.7	0.1	0.7
36710020	1		8.56	14.5	79.9	3.7	1.2	0.1	0.6
		Mean	10.584	13.66	81.20	2.84	1.42	0.16	0.76
		SD	1.786	5.70	6.51	0.59	0.75	0.05	0.13
36710052	4		12.17	25.9	67.7	3.8	1.4	0.2	0.9
36710054	4		5.47	11.5	83.4	3.2	0.8	0.1	1.0
36710056	4		9.70	5.9	89.3	2.6	1.2	0.2	0.8
36710058	4		8.90	7.1	88.4	2.6	0.9	0.2	0.8
36710060	4		8.36	8.2	86.3	3.6	1.1	0.1	0.7
		Mean	8.920	11.72	83.02	3.16	1.08	0.16	0.84
		SD	2.418	8.20	8.86	0.55	0.24	0.05	0.11

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Haematology - At the end of recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		RBC 10^12/l	HGB g/dl	HCT %	MCV fl	MCH pg	MCHC g/dl
36710011	1		7.83	15.1	41.4	52.8	19.3	36.5
36710013	1		7.54	14.4	40.0	53.0	19.1	36.1
36710015	1		7.39	14.4	38.9	52.6	19.5	37.1
36710017	1		7.59	14.0	39.3	51.8	18.4	35.5
36710019	1		7.31	14.1	38.9	53.2	19.3	36.2
		Mean	7.532	14.40	39.70	52.68	19.12	36.28
		SD	0.201	0.43	1.05	0.54	0.43	0.58
36710051	4		6.83	13.4	36.8	53.9	19.7	36.5
36710053	4		6.84	13.2	36.3	53.0	19.3	36.4
36710055	4		7.26	14.0	38.5	53.0	19.3	36.4
36710057	4		7.41	14.1	39.5	53.3	19.0	35.6
36710059	4		6.95	12.8	36.4	52.4	18.5	35.2
		Mean	7.058	13.50	37.50	53.12	19.16	36.02
		SD	0.263	0.55	1.43	0.54	0.44	0.58

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Haematology - At the end of recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		PLT 10^9/l	PT sec
36710011	1		871	16.4
36710013	1		916	16.7
36710015	1		964	17.1
36710017	1		872	17.1
36710019	1		848	17.6
		Mean	894.2	16.98
		SD	46.1	0.45
36710051	4		976	16.5
36710053	4		756	15.8
36710055	4		937	16.3
36710057	4		901	16.4
36710059	4		794	16.9
		Mean	872.8	16.38
		SD	94.1	0.40

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 7.2 - Haematology - At the end of recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		WBC 10^9/l	NEU %	LYM %	MON %	EOS %	BAS %	LUC %
36710011	1		11.54	9.0	84.0	4.1	1.3	0.3	1.2
36710013	1		8.23	7.9	84.2	4.9	1.4	0.1	1.5
36710015	1		7.10	8.2	84.4	3.8	2.4	0.2	1.1
36710017	1		8.31	7.7	85.1	4.1	1.7	0.2	1.2
36710019	1		8.10	10.2	84.5	3.0	1.2	0.2	1.0
		Mean	8.656	8.60	84.44	3.98	1.60	0.20	1.20
		SD	1.684	1.02	0.42	0.68	0.48	0.07	0.19
36710051	4		7.70	7.3	87.7	3.3	0.7	0.1	0.9
36710053	4		8.29	5.1	88.3	3.2	1.2	0.2	1.9
36710055	4		6.49	10.2	85.2	3.0	0.9	0.1	0.7
36710057	4		7.89	5.8	89.8	2.2	1.4	0.1	0.8
36710059	4		8.28	10.8	83.7	3.3	1.0	0.2	1.0
		Mean	7.730	7.84	86.94	3.00	1.04	0.14	1.06
		SD	0.738	2.56	2.46	0.46	0.27	0.05	0.48

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		AP U/l	ALT U/l	AST U/l	GGT U/l	BILT mg/dl	CHOL mg/dl	TRI mg/dl	GLU mg/dl
36710002	1		215.1	30.5	75.2	0.10	0.11	72.1	34.0	100.5
36710004	1		313.3	36.2	92.2	0.10	0.09	75.8	48.9	127.3
36710006	1		220.1	28.6	86.6	0.20	0.11	65.2	26.4	91.0
36710008	1		271.6	31.2	79.0	0.20	0.13	93.9	45.5	99.6
36710010	1		269.5	31.3	72.5	0.50	0.12	64.6	34.5	114.5
		Mean	257.92	31.56	81.10	0.220	0.112	74.32	37.86	106.58
		SD	40.78	2.81	8.16	0.164	0.015	11.92	9.19	14.32
36710022	2		249.9	41.5	72.4	0.00	0.09	42.6	33.7	123.4
36710024	2		227.1	26.5	69.0	0.00	0.07	56.7	15.0	113.6
36710026	2		233.5	29.0	73.9	0.30	0.02	35.4	24.2	149.3
36710028	2		264.3	29.7	72.3	0.00	0.10	58.4	29.9	99.7
36710030	2		229.5	43.0	88.8	0.70	0.09	52.7	33.1	119.9
		Mean	240.86	33.94	75.28	0.200	0.074	49.16	27.18	121.18
		SD	15.84	7.70	7.77	0.308	0.032	9.84	7.78	18.14
36710032	3		288.7	46.2	86.1	0.00	0.04	52.3	16.7	114.7
36710034	3		353.6	253.4	195.1	0.10	0.07	65.4	17.6	109.8
36710036	3		259.8	73.5	102.5	0.00	0.09	63.9	17.8	133.2
36710038	3		301.5	43.9	89.0	0.00	0.09	49.4	20.1	117.0
36710040	3		312.8	229.0	166.8	0.00	0.09	54.1	20.3	122.2
		Mean	303.28	129.20	127.90	0.020	0.076	57.02	18.50	119.38
		SD	34.38	103.26	49.84	0.045	0.022	7.18	1.61	8.92
36710042	4		260.4	117.9	140.5	0.00	0.23	85.5	39.4	125.3
36710044	4		339.3	82.1	120.0	0.10	0.20	66.9	35.5	135.9
36710046	4		410.8	84.0	99.4	0.10	0.13	76.5	34.3	121.3
36710048	4		391.8	68.8	107.3	0.00	0.17	85.2	38.0	116.5
36710050	4		306.8	150.3	184.3	0.10	0.22	78.5	34.0	122.0
		Mean	341.82	100.62	130.30	0.060	0.190	78.52	36.24	124.20
		SD	61.48	33.16	33.95	0.055	0.041	7.62	2.37	7.26

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		UREA mg/dl	CREA mg/dl	CL mmol/l	PHOS mg/dl	CA mmol/l	Na mmol/l	K mmol/l
36710002	1		43.2	0.31	92.7	8.3	2.51	144.2	4.12
36710004	1		41.2	0.32	91.8	9.0	2.62	145.0	3.77
36710006	1		41.2	0.30	93.3	8.3	2.72	143.5	3.92
36710008	1		55.9	0.43	92.3	8.4	2.66	144.1	3.70
36710010	1		45.9	0.32	94.4	8.7	2.61	144.1	3.86
		Mean	45.48	0.336	92.90	8.54	2.624	144.18	3.874
		SD	6.14	0.053	1.00	0.33	0.077	0.54	0.161
36710022	2		43.3	0.36	92.8	8.7	2.67	142.5	3.73
36710024	2		48.9	0.30	94.8	8.3	2.71	142.2	3.80
36710026	2		47.9	0.29	94.4	8.1	2.55	141.1	3.68
36710028	2		46.0	0.33	93.7	8.6	2.63	146.1	3.77
36710030	2		52.3	0.33	92.3	9.0	2.62	143.1	3.62
		Mean	47.68	0.322	93.60	8.56	2.636	143.00	3.720
		SD	3.35	0.028	1.05	0.34	0.060	1.88	0.072
36710032	3		61.0	0.33	93.2	7.4	2.58	149.2	4.01
36710034	3		50.0	0.27	94.4	7.6	2.62	150.3	3.97
36710036	3		48.1	0.31	92.3	8.0	2.66	148.9	4.14
36710038	3		52.7	0.30	93.8	7.9	2.62	151.9	3.82
36710040	3		51.3	0.37	94.1	8.0	2.58	151.0	4.04
		Mean	52.62	0.316	93.56	7.78	2.612	150.26	3.996
		SD	4.98	0.037	0.83	0.27	0.033	1.25	0.117
36710042	4		64.3	0.27	95.6	6.4	2.22	147.3	4.46
36710044	4		71.1	0.32	94.0	6.3	2.54	145.1	4.13
36710046	4		64.1	0.28	94.4	7.0	2.56	145.5	4.15
36710048	4		70.9	0.29	95.6	7.4	2.48	146.5	4.18
36710050	4		66.9	0.33	95.1	6.3	1.76	146.1	5.52
		Mean	67.46	0.298	94.94	6.68	2.312	146.10	4.488
		SD	3.42	0.026	0.72	0.50	0.337	0.86	0.592

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		PROT g/dl	ALB g/dl	GLO g/dl	AGR
36710002	1		6.4	4.0	2.4	1.7
36710004	1		6.5	4.0	2.5	1.6
36710006	1		6.5	4.0	2.5	1.6
36710008	1		6.7	4.1	2.6	1.6
36710010	1		6.2	3.9	2.3	1.7
		Mean	6.46	4.00	2.46	1.63
		SD	0.18	0.07	0.11	0.05
36710022	2		6.0	3.9	2.1	1.9
36710024	2		5.9	3.8	2.1	1.8
36710026	2		5.6	3.7	1.9	1.9
36710028	2		6.1	3.8	2.3	1.7
36710030	2		5.9	3.7	2.2	1.7
		Mean	5.90	3.78	2.12	1.79
		SD	0.19	0.08	0.15	0.12
36710032	3		6.4	3.9	2.5	1.6
36710034	3		6.0	3.8	2.2	1.7
36710036	3		6.2	4.0	2.2	1.8
36710038	3		6.2	4.2	2.0	2.1
36710040	3		6.0	4.0	2.0	2.0
		Mean	6.16	3.98	2.18	1.84
		SD	0.17	0.15	0.20	0.21
36710042	4		4.7	3.3	1.4	2.4
36710044	4		5.6	3.6	2.0	1.8
36710046	4		5.6	3.9	1.7	2.3
36710048	4		6.2	3.5	2.7	1.3
36710050	4		4.9	3.2	1.7	1.9
		Mean	5.40	3.50	1.90	1.93
		SD	0.60	0.27	0.49	0.43

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		AP U/l	ALT U/l	AST U/l	GGT U/l	BILT mg/dl	CHOL mg/dl	TRI mg/dl	GLU mg/dl
36710001	1		191.9	28.5	72.7	4.30	0.10	78.4	25.2	108.6
36710003	1		191.8	29.0	66.1	0.40	0.09	76.3	36.1	119.0
36710005	1		227.5	32.8	73.8	0.10	0.06	66.8	22.3	115.5
36710007	1		250.0	35.6	92.6	1.30	0.10	81.6	38.2	99.0
36710009	1		178.0	29.8	99.2	0.50	0.10	99.6	34.7	115.8
		Mean	207.84	31.14	80.88	1.320	0.090	80.54	31.30	111.58
		SD	29.86	3.00	14.22	1.724	0.017	12.00	7.08	7.99
36710021	2		178.7	30.5	72.3	1.90	0.07	82.6	28.0	87.8
36710023	2		156.9	23.9	62.7	1.10	0.06	62.3	19.5	119.8
36710025	2		155.8	27.2	85.4	1.40	0.07	72.0	37.3	100.3
36710029	2		211.1	30.5	71.8	1.50	0.05	65.4	19.6	114.7
		Mean	175.63	28.03	73.05	1.475	0.063	70.58	26.10	105.65
		SD	25.89	3.16	9.34	0.330	0.010	8.98	8.46	14.48
36710031	3		234.5	40.0	73.7	0.70	0.06	88.9	29.7	106.8
36710033	3		216.3	44.0	77.8	1.30	0.02	65.6	23.9	119.9
36710035	3		211.0	29.2	80.1	0.80	0.03	69.5	33.8	114.7
36710037	3		267.7	42.7	86.9	0.70	0.04	62.9	26.5	111.1
36710039	3		259.3	67.3	102.5	0.50	0.03	69.8	24.7	132.8
		Mean	237.76	44.64	84.20	0.800	0.036	71.34	27.72	117.06
		SD	25.24	13.94	11.29	0.300	0.015	10.23	4.06	10.03
36710041	4		280.5	56.4	98.6	4.80	0.10	80.8	38.8	125.3
36710043	4		224.6	43.1	89.2	5.00	0.05	58.3	22.9	130.2
36710045	4		144.8	24.2	67.0	0.80	0.04	76.1	30.1	142.5
36710047	4		246.5	31.7	74.0	0.10	0.06	91.2	25.1	136.1
36710049	4		205.1	38.9	82.7	1.00	0.05	70.9	36.1	134.9
		Mean	220.30	38.86	82.30	2.340	0.060	75.46	30.60	133.80
		SD	50.65	12.16	12.41	2.362	0.023	12.16	6.84	6.47

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		UREA mg/dl	CREA mg/dl	CL mmol/l	PHOS mg/dl	CA mmol/l	Na mmol/l	K mmol/l
36710001	1		47.2	0.41	94.3	7.3	2.65	144.4	3.46
36710003	1		47.0	0.41	93.0	7.4	2.61	143.3	3.35
36710005	1		56.0	0.50	95.2	7.3	2.60	143.7	3.32
36710007	1		53.5	0.48	95.3	8.1	2.64	143.6	4.06
36710009	1		40.8	0.43	93.9	7.2	2.57	144.7	4.31
		Mean	48.90	0.446	94.34	7.47	2.614	143.94	3.700
		SD	5.99	0.042	0.96	0.37	0.032	0.59	0.454
36710021	2		50.6	0.43	94.9	7.2	2.75	142.9	3.43
36710023	2		46.0	0.38	94.4	7.5	2.75	142.5	3.58
36710025	2		46.2	0.47	95.9	7.3	2.68	143.9	3.70
36710029	2		46.7	0.36	97.1	8.0	2.64	144.5	3.71
		Mean	47.38	0.410	95.58	7.51	2.705	143.45	3.605
		SD	2.17	0.050	1.19	0.36	0.054	0.91	0.131
36710031	3		47.0	0.45	94.5	6.4	2.81	145.1	3.76
36710033	3		58.0	0.45	96.2	7.0	2.64	146.0	3.72
36710035	3		39.4	0.40	97.4	6.9	2.50	146.8	3.10
36710037	3		52.3	0.41	97.9	7.1	2.49	145.4	3.42
36710039	3		49.8	0.41	96.7	7.4	2.51	145.0	3.17
		Mean	49.30	0.424	96.54	6.97	2.590	145.66	3.434
		SD	6.86	0.024	1.31	0.37	0.137	0.75	0.304
36710041	4		61.8	0.36	96.8	6.5	2.58	146.3	3.42
36710043	4		60.5	0.35	96.4	7.2	2.67	143.0	3.88
36710045	4		51.1	0.37	94.2	6.8	2.79	144.3	3.83
36710047	4		55.5	0.38	96.3	6.2	2.71	142.7	3.45
36710049	4		75.3	0.44	96.3	7.2	2.57	142.1	3.18
		Mean	60.84	0.380	96.00	6.79	2.664	143.68	3.552
		SD	9.13	0.035	1.03	0.42	0.092	1.67	0.296

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.1 - Clinical chemistry - At the end of treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		PROT g/dl	ALB g/dl	GLO g/dl	AGR
36710001	1		6.1	4.1	2.0	2.1
36710003	1		6.2	4.2	2.0	2.1
36710005	1		6.1	4.0	2.1	1.9
36710007	1		6.6	4.1	2.5	1.6
36710009	1		6.3	4.4	1.9	2.3
		Mean	6.26	4.16	2.10	2.00
		SD	0.21	0.15	0.23	0.25
36710021	2		6.3	4.0	2.3	1.7
36710023	2		6.8	4.4	2.4	1.8
36710025	2		6.3	4.3	2.0	2.2
36710029	2		6.2	4.0	2.2	1.8
		Mean	6.40	4.18	2.23	1.89
		SD	0.27	0.21	0.17	0.18
36710031	3		6.8	4.6	2.2	2.1
36710033	3		6.7	4.4	2.3	1.9
36710035	3		6.6	4.3	2.3	1.9
36710037	3		6.5	4.5	2.0	2.3
36710039	3		6.4	4.2	2.2	1.9
		Mean	6.60	4.40	2.20	2.01
		SD	0.16	0.16	0.12	0.16
36710041	4		6.2	4.2	2.0	2.1
36710043	4		6.4	4.6	1.8	2.6
36710045	4		6.5	4.5	2.0	2.3
36710047	4		6.3	4.4	1.9	2.3
36710049	4		5.9	4.2	1.7	2.5
		Mean	6.26	4.38	1.88	2.34
		SD	0.23	0.18	0.13	0.18

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Clinical chemistry - At the end of recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		AP U/l	ALT U/l	AST U/l	GGT U/l	BILT mg/dl	CHOL mg/dl	TRI mg/dl	GLU mg/dl
36710012	1		202.3	34.2	59.4	0.20	0.10	70.5	47.1	115.5
36710014	1		238.1	31.0	59.3	2.40	0.10	79.6	47.5	118.5
36710016	1		202.2	32.0	63.2	0.30	0.15	87.4	42.2	122.3
36710018	1		198.1	33.2	62.8	1.70	0.14	67.5	40.1	125.1
36710020	1		240.3	29.5	62.7	1.00	0.15	72.8	36.3	116.7
		Mean	216.20	31.98	61.48	1.120	0.128	75.56	42.64	119.62
		SD	21.08	1.84	1.95	0.936	0.026	7.98	4.75	4.00
36710052	4		255.7	30.6	58.9	1.00	0.13	102.0	29.9	128.9
36710054	4		303.6	24.6	51.9	0.90	0.34	145.2	17.2	124.7
36710056	4		296.1	31.1	63.2	1.70	0.24	155.7	21.7	133.5
36710058	4		329.0	52.6	74.5	0.40	0.15	117.0	19.9	151.1
36710060	4		342.8	37.0	55.7	0.80	0.13	143.9	29.0	182.3
		Mean	305.44	35.18	60.84	0.960	0.198	132.76	23.54	144.10
		SD	33.60	10.68	8.69	0.472	0.091	22.36	5.64	23.60

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Clinical chemistry - At the end of recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		UREA mg/dl	CREA mg/dl	CL mmol/l	PHOS mg/dl	CA mmol/l	Na mmol/l	K mmol/l
36710012	1		35.8	0.30	92.7	7.9	2.70	147.5	4.01
36710014	1		47.0	0.32	93.3	8.1	2.77	147.5	4.16
36710016	1		51.0	0.37	91.9	8.1	2.80	147.0	4.45
36710018	1		39.0	0.36	93.0	8.4	2.51	146.4	4.62
36710020	1		49.8	0.39	93.7	8.2	2.65	147.7	4.15
		Mean	44.52	0.348	92.92	8.12	2.686	147.22	4.278
		SD	6.76	0.037	0.68	0.18	0.115	0.53	0.249
36710052	4		54.1	0.19	94.9	5.9	2.62	145.4	4.37
36710054	4		71.3	0.23	95.3	7.5	2.50	142.3	4.50
36710056	4		61.2	0.23	95.1	6.1	2.72	145.2	3.53
36710058	4		60.9	0.25	94.1	8.5	2.18	145.2	5.61
36710060	4		53.1	0.25	91.8	7.1	2.72	142.6	4.44
		Mean	60.12	0.230	94.24	7.00	2.548	144.14	4.490
		SD	7.29	0.024	1.44	1.09	0.225	1.55	0.740

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Clinical chemistry - At the end of recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		PROT g/dl	ALB g/dl	GLO g/dl	AGR
36710012	1		6.4	3.9	2.5	1.6
36710014	1		6.4	3.9	2.5	1.6
36710016	1		6.5	4.0	2.5	1.6
36710018	1		6.6	3.7	2.9	1.3
36710020	1		6.4	3.9	2.5	1.6
		Mean	6.46	3.88	2.58	1.51
		SD	0.09	0.11	0.18	0.13
36710052	4		5.5	3.6	1.9	1.9
36710054	4		5.1	3.4	1.7	2.0
36710056	4		5.8	3.9	1.9	2.1
36710058	4		5.8	4.0	1.8	2.2
36710060	4		6.5	4.3	2.2	2.0
		Mean	5.74	3.84	1.90	2.02
		SD	0.51	0.35	0.19	0.12

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Clinical chemistry - At the end of recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		AP U/l	ALT U/l	AST U/l	GGT U/l	BILT mg/dl	CHOL mg/dl	TRI mg/dl	GLU mg/dl
36710011	1		171.3	30.0	86.3	2.10	0.17	87.1	43.8	94.9
36710013	1		142.7	26.9	70.5	0.20	0.17	77.6	41.0	101.8
36710015	1		179.7	26.2	76.1	1.20	0.16	77.2	36.3	105.2
36710017	1		158.0	27.1	74.2	1.10	0.17	59.9	46.0	104.1
36710019	1		170.3	22.2	74.0	1.70	0.15	48.5	50.6	112.7
		Mean	164.40	26.48	76.22	1.260	0.164	70.06	43.54	103.74
		SD	14.39	2.80	5.99	0.716	0.009	15.54	5.36	6.41
36710051	4		118.0	28.4	54.8	0.70	0.09	81.5	27.8	123.4
36710053	4		165.8	28.5	55.7	2.00	0.09	73.1	27.9	147.1
36710055	4		164.7	23.2	51.9	0.30	0.10	81.2	28.4	117.4
36710057	4		135.1	27.9	54.1	1.30	0.12	77.8	37.0	120.5
36710059	4		120.1	35.8	55.0	0.30	0.12	76.8	36.8	170.5
		Mean	140.74	28.76	54.30	0.920	0.104	78.08	31.58	135.78
		SD	23.33	4.51	1.46	0.729	0.015	3.46	4.86	22.68

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Clinical chemistry - At the end of recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		UREA mg/dl	CREA mg/dl	CL mmol/l	PHOS mg/dl	CA mmol/l	Na mmol/l	K mmol/l
36710011	1		75.8	0.65	95.8	7.0	2.77	147.7	3.26
36710013	1		70.2	0.57	94.7	7.3	2.67	148.5	3.05
36710015	1		60.3	0.56	95.1	7.5	2.63	147.9	3.18
36710017	1		73.3	0.50	94.7	7.8	2.71	148.3	3.46
36710019	1		59.5	0.48	94.7	7.0	2.67	147.2	3.66
		Mean	67.82	0.552	95.00	7.32	2.690	147.92	3.322
		SD	7.50	0.067	0.48	0.32	0.053	0.51	0.240
36710051	4		74.5	0.40	94.2	6.7	2.80	145.6	3.85
36710053	4		63.7	0.37	92.4	6.9	2.79	144.5	3.49
36710055	4		64.0	0.39	94.0	6.6	2.80	145.7	3.81
36710057	4		50.0	0.31	93.9	6.8	2.82	145.4	3.49
36710059	4		53.1	0.32	94.9	7.0	2.46	146.2	3.97
		Mean	61.06	0.358	93.88	6.80	2.734	145.48	3.722
		SD	9.77	0.041	0.91	0.18	0.154	0.62	0.220

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 8.2 - Clinical chemistry - At the end of recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		PROT g/dl	ALB g/dl	GLO g/dl	AGR
36710011	1		6.6	4.3	2.3	1.9
36710013	1		6.2	4.2	2.0	2.1
36710015	1		6.2	4.1	2.1	2.0
36710017	1		5.9	4.1	1.8	2.3
36710019	1		6.1	3.9	2.2	1.8
		Mean	6.20	4.12	2.08	1.99
		SD	0.25	0.15	0.19	0.20
36710051	4		6.5	4.7	1.8	2.6
36710053	4		6.1	4.4	1.7	2.6
36710055	4		6.9	4.8	2.1	2.3
36710057	4		6.5	4.6	1.9	2.4
36710059	4		6.0	4.0	2.0	2.0
		Mean	6.40	4.50	1.90	2.38
		SD	0.36	0.32	0.16	0.25

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		VOL ml	SG
36710002	1		6.0	1.015
36710004	1		5.0	1.015
36710006	1		5.5	1.015
36710008	1		6.0	1.025
36710010	1		6.5	1.020
		Mean	5.80	1.0180
		SD	0.57	0.0045
36710022	2		5.0	1.020
36710024	2		7.0	1.020
36710026	2		7.0	1.030
36710028	2		7.5	1.020
36710030	2		6.5	1.025
		Mean	6.60	1.0230
		SD	0.96	0.0045
36710032	3		6.0	1.010
36710034	3		8.0	1.005
36710036	3		8.5	1.020
36710038	3		6.0	1.010
36710040	3		5.5	1.015
		Mean	6.80	1.0120
		SD	1.35	0.0057
36710042	4		8.0	1.015
36710044	4		7.5	1.020
36710046	4		7.0	1.010
36710048	4		6.0	1.015
36710050	4		6.5	1.015
		Mean	7.00	1.0150
		SD	0.79	0.0035

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
36710002	1	0	0	7.0	0	30	0.00	150	0.0
36710004	1	0	0	6.5	0	30	0.00	80	0.0
36710006	1	0	0	7.5	50	100	0.00	150	2.0
36710008	1	0	0	6.5	0	30	0.00	150	0.0
36710010	1	0	0	7.0	0	30	0.00	40	0.0
36710022	2	0	0	6.0	0	15	0.00	0	0.0
36710024	2	0	0	7.0	0	15	0.00	0	0.0
36710026	2	0	0	6.5	0	15	0.06	0	0.0
36710028	2	0	0	6.5	0	30	0.00	0	0.0
36710030	2	0	0	6.5	0	15	0.00	0	0.0
36710032	3	0	0	7.5	0	30	0.00	15	0.0
36710034	3	0	0	7.5	0	30	0.00	15	0.0
36710036	3	0	0	7.0	0	30	0.00	15	0.0
36710038	3	0	0	7.5	0	100	0.00	0	0.0
36710040	3	0	0	7.5	0	15	0.00	40	0.0
36710042	4	0	0	7.0	0	15	0.00	0	0.0
36710044	4	0	0	6.5	0	30	0.00	40	0.0
36710046	4	0	0	6.5	0	15	0.06	15	0.0
36710048	4	0	0	7.0	0	30	0.00	15	0.0
36710050	4	0	0	6.5	0	30	0.00	15	0.0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	URO mg/dl
36710002	1	1.0
36710004	1	1.0
36710006	1	4.0
36710008	1	1.0
36710010	1	1.0
36710022	2	1.0
36710024	2	1.0
36710026	2	1.0
36710028	2	1.0
36710030	2	1.0
36710032	3	1.0
36710034	3	1.0
36710036	3	1.0
36710038	3	1.0
36710040	3	1.0
36710042	4	1.0
36710044	4	1.0
36710046	4	1.0
36710048	4	1.0
36710050	4	1.0

[redacted]-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
36710002	1	1	0	0	1	1	0
36710004	1	1	0	0	1	1	0
36710006	1	1	0	0	0	0	0
36710008	1	1	1	0	0	1	0
36710010	1	1	0	0	1	1	0
36710022	2	0	0	0	0	0	0
36710024	2	1	0	0	0	0	0
36710026	2	1	0	0	0	0	0
36710028	2	2	0	0	0	0	0
36710030	2	1	0	0	0	0	0
36710032	3	1	0	0	0	0	0
36710034	3	1	0	0	0	0	0
36710036	3	1	0	0	1	1	0
36710038	3	1	0	0	1	0	0
36710040	3	1	0	0	1	0	0
36710042	4	1	0	0	2	1	0
36710044	4	1	0	0	1	1	0
36710046	4	1	0	0	1	1	0
36710048	4	1	0	0	1	1	0
36710050	4	1	0	0	0	0	0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		VOL ml	SG
36710001	1		6.5	1.020
36710003	1		5.0	1.010
36710005	1		6.5	1.015
36710007	1		7.5	1.015
36710009	1		6.0	1.015
		Mean	6.30	1.0150
		SD	0.91	0.0035
36710021	2		9.0	1.015
36710023	2		7.5	1.020
36710025	2		8.0	1.015
36710029	2		4.5	1.020
		Mean	7.25	1.0175
		SD	1.94	0.0029
36710031	3		4.5	1.030
36710033	3		2.0	1.015
36710035	3		5.5	1.020
36710037	3		5.0	1.020
36710039	3		7.0	1.025
		Mean	4.80	1.0220
		SD	1.82	0.0057
36710041	4		6.0	1.030
36710043	4		5.5	1.015
36710045	4		1.5	1.030
36710047	4		3.5	1.030
36710049	4		4.5	1.030
		Mean	4.20	1.0270
		SD	1.79	0.0067

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
36710001	1	0	0	6.5	0	0	0.00	0	0.0
36710003	1	0	0	7.0	0	15	0.00	0	0.0
36710005	1	0	0	7.0	0	15	0.00	0	0.0
36710007	1	0	0	6.5	0	0	0.00	0	0.0
36710009	1	0	0	7.0	0	15	0.00	0	0.0
36710021	2	0	0	7.0	0	15	0.00	0	0.0
36710023	2	0	0	7.0	0	0	0.00	0	0.0
36710025	2	0	0	7.0	0	0	0.00	0	0.0
36710029	2	0	0	6.5	0	30	0.00	0	0.0
36710031	3	0	0	6.5	50	15	0.00	0	0.0
36710033	3	0	0	7.0	0	15	0.00	0	0.0
36710035	3	0	0	7.0	0	15	0.00	0	0.0
36710037	3	0	0	6.5	0	15	0.00	0	0.0
36710039	3	0	0	6.5	0	0	0.00	0	0.0
36710041	4	0	0	6.5	0	0	0.00	0	0.0
36710043	4	0	0	7.0	0	15	0.00	0	0.0
36710045	4	0	0	6.5	0	30	0.00	15	0.0
36710047	4	0	0	6.5	0	0	0.00	0	0.0
36710049	4	0	0	6.5	0	15	0.00	0	0.0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	URO mg/dl
36710001	1	1.0
36710003	1	1.0
36710005	1	1.0
36710007	1	1.0
36710009	1	1.0
36710021	2	1.0
36710023	2	1.0
36710025	2	1.0
36710029	2	1.0
36710031	3	2.0
36710033	3	1.0
36710035	3	1.0
36710037	3	1.0
36710039	3	1.0
36710041	4	1.0
36710043	4	1.0
36710045	4	2.0
36710047	4	1.0
36710049	4	1.0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.1 - Urinalysis - At the end of treatment - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
36710001	1	1	0	0	1	0	0
36710003	1	1	0	0	1	0	0
36710005	1	1	0	0	1	0	0
36710007	1	1	0	0	0	0	0
36710009	1	1	0	0	1	0	0
36710021	2	1	0	0	0	0	0
36710023	2	1	0	0	1	0	0
36710025	2	1	0	0	1	0	0
36710029	2	1	0	0	1	0	0
36710031	3	1	0	0	0	0	0
36710033	3	1	0	0	1	0	0
36710035	3	1	0	0	1	0	0
36710037	3	1	0	0	0	0	0
36710039	3	1	0	0	0	0	0
36710041	4	0	0	0	0	0	0
36710043	4	0	0	0	0	0	0
36710045	4	0	0	0	1	0	0
36710047	4	1	0	0	0	0	0
36710049	4	0	0	0	0	0	0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group		VOL ml	SG
36710012	1		5.0	1.010
36710014	1		10.0	1.010
36710016	1		13.5	1.010
36710018	1		9.0	1.010
36710020	1		5.5	1.005
		Mean	8.60	1.0090
		SD	3.49	0.0022
36710052	4		4.0	1.025
36710054	4		9.5	1.010
36710056	4		4.0	1.025
36710058	4		7.0	1.020
36710060	4		11.0	1.015
		Mean	7.10	1.0190
		SD	3.17	0.0065

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
36710012	1	1	0	8.0	0	30	0.00	15	0.0
36710014	1	1	0	7.5	0	30	0.00	0	0.0
36710016	1	1	0	7.5	0	100	0.00	0	0.0
36710018	1	1	0	7.5	0	100	0.00	0	0.0
36710020	1	1	0	7.5	0	30	0.00	0	0.0
36710052	4	0	0	6.5	0	15	0.00	0	0.0
36710054	4	1	0	7.5	0	0	0.00	0	0.0
36710056	4	0	0	7.0	0	30	0.00	0	0.0
36710058	4	1	0	6.5	0	30	0.00	0	0.0
36710060	4	0	0	7.0	0	15	0.00	0	0.0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	URO mg/dl
36710012	1	1.0
36710014	1	1.0
36710016	1	1.0
36710018	1	1.0
36710020	1	1.0
36710052	4	1.0
36710054	4	1.0
36710056	4	1.0
36710058	4	1.0
36710060	4	1.0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
36710012	1	1	1	0	2	1	0
36710014	1	0	0	0	1	1	0
36710016	1	2	0	0	1	1	0
36710018	1	1	1	0	1	1	0
36710020	1	1	0	0	1	1	0
36710052	4	2	1	0	1	0	0
36710054	4	1	1	0	0	1	0
36710056	4	1	1	0	0	0	0
36710058	4	1	1	0	1	0	0
36710060	4	1	0	0	1	1	0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group		VOL ml	SG
36710011	1		2.0	1.030
36710013	1		4.0	1.025
36710015	1		6.0	1.010
36710017	1		2.0	1.020
36710019	1		3.0	1.020
		Mean	3.40	1.0210
		SD	1.67	0.0074
36710051	4		4.5	1.025
36710053	4		9.0	1.020
36710055	4		5.0	1.030
36710057	4		3.0	1.030
36710059	4		6.0	1.030
		Mean	5.50	1.0270
		SD	2.24	0.0045

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	APP	RED	PH	GLU mg/dl	PRO mg/dl	BLD mg/dl	KET mg/dl	BIL mg/dl
36710011	1	0	0	6.5	0	30	0.00	0	0.0
36710013	1	0	0	7.0	0	15	0.00	0	0.0
36710015	1	0	0	7.5	0	0	0.00	0	0.0
36710017	1	0	0	7.0	0	30	0.00	0	0.5
36710019	1	0	0	7.0	0	30	0.00	0	0.0
36710051	4	0	0	6.5	0	0	0.00	0	0.0
36710053	4	0	0	7.0	0	0	0.00	0	0.0
36710055	4	0	0	6.5	0	15	0.00	0	0.0
36710057	4	0	0	6.5	0	0	0.00	0	0.0
36710059	4	0	0	6.5	0	0	0.00	0	0.0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	URO mg/dl
36710011	1	2.0
36710013	1	1.0
36710015	1	1.0
36710017	1	2.0
36710019	1	1.0
36710051	4	1.0
36710053	4	1.0
36710055	4	1.0
36710057	4	1.0
36710059	4	1.0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 9.2 - Urinalysis - At the end of recovery - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	EPI	LEU	ERY	CRY	SPE	ABN
36710011	1	1	0	0	1	0	0
36710013	1	1	0	0	0	0	0
36710015	1	1	1	0	1	0	0
36710017	1	2	1	0	1	0	0
36710019	1	1	1	0	0	0	0
36710051	4	2	1	0	0	0	0
36710053	4	1	1	0	1	0	0
36710055	4	2	1	0	1	0	0
36710057	4	1	1	0	1	0	0
36710059	4	2	1	0	1	0	0

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
36710002	1	335.6	0.053	1.78	1.056	1.24	2.08	8.83
36710004	1	361.2	0.043	1.77	1.044	1.20	2.22	10.10
36710006	1	348.9	0.064	1.77	1.127	1.27	2.23	9.76
36710008	1	340.7	0.042	1.84	1.123	1.34	2.03	8.89
36710010	1	348.3	0.041	1.88	1.099	1.12	2.17	8.67
	Mean	346.94	0.0486	1.806	1.0898	1.234	2.145	9.251
	SD	9.70	0.0099	0.050	0.0381	0.080	0.087	0.638
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710022	2	339.9	0.049	1.84	1.003	1.12	2.28	10.66
36710024	2	317.6	0.046	1.73	1.088	1.11	2.04	9.73
36710026	2	320.4	0.054	1.78	1.107	1.17	2.09	9.58
36710028	2	340.6	0.050	1.82	1.098	1.29	2.13	10.87
36710030	2	350.9	0.050	1.87	1.240	1.16	2.15	11.48
	Mean	333.88	0.0498	1.806	1.1072	1.168	2.140	10.462
	SD	14.30	0.0029	0.054	0.0851	0.070	0.091	0.799
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710032	3	343.8	0.038	1.84	1.002	1.17	2.23	14.57
36710034	3	346.7	0.049	1.80	1.094	1.33	2.50	14.31
36710036	3	354.8	0.071	1.84	1.237	1.25	2.59	14.94
36710038	3	329.1	0.044	1.80	1.056	1.17	2.24	12.83
36710040	3	331.5	0.048	1.84	1.099	1.24	2.24	14.70
	Mean	341.18	0.0500	1.824	1.0976	1.233	2.358	14.270
	SD	10.75	0.0125	0.023	0.0871	0.068	0.173	0.837
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710042	4	246.7	0.041	1.79	1.156	0.89	2.01	15.13
36710044	4	291.8	0.046	1.83	1.053	0.93	2.08	18.27
36710046	4	278.7	0.041	1.62	0.997	0.87	2.14	17.27
36710048	4	307.7	0.047	1.74	1.042	1.08	2.41	18.15
36710050	4	260.6	0.039	1.82	1.093	0.83	1.80	16.15
	Mean	277.10	0.0428	1.761	1.0682	0.917	2.087	16.995
	SD	24.25	0.0035	0.085	0.0598	0.096	0.220	1.345
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus	Thyroid
36710002	1	335.6	0.901	4.084	0.493	0.028
36710004	1	361.2	0.865	3.572	0.553	0.022
36710006	1	348.9	1.004	3.815	0.490	0.027
36710008	1	340.7	0.818	3.626	0.625	0.025
36710010	1	348.3	0.849	3.592	0.465	0.023
	Mean	346.94	0.8874	3.7378	0.5252	0.0250
	SD	9.70	0.0717	0.2163	0.0645	0.0025
	(n)	(5)	(5)	(5)	(5)	(5)
36710022	2	339.9	0.900	3.676	0.654	0.027
36710024	2	317.6	0.699	3.608	0.542	0.029
36710026	2	320.4	0.686	3.784	0.431	0.026
36710028	2	340.6	0.788	3.925	0.663	0.026
36710030	2	350.9	0.933	3.898	0.464	0.021
	Mean	333.88	0.8012	3.7782	0.5508	0.0258
	SD	14.30	0.1129	0.1372	0.1063	0.0029
	(n)	(5)	(5)	(5)	(5)	(5)
36710032	3	343.8	0.718	3.470	0.552	0.027
36710034	3	346.7	0.889	3.827	0.494	0.027
36710036	3	354.8	0.960	3.936	0.636	0.027
36710038	3	329.1	0.748	3.967	0.482	0.026
36710040	3	331.5	0.730	3.632	0.566	0.027
	Mean	341.18	0.8090	3.7664	0.5460	0.0268
	SD	10.75	0.1089	0.2113	0.0619	0.0004
	(n)	(5)	(5)	(5)	(5)	(5)
36710042	4	246.7	0.436	3.784	0.186	0.024
36710044	4	291.8	0.707	3.676	0.308	0.026
36710046	4	278.7	0.500	3.618	0.399	0.023
36710048	4	307.7	0.613	3.713	0.418	0.029
36710050	4	260.6	0.485	3.314	0.237	0.024
	Mean	277.10	0.5482	3.6210	0.3096	0.0252
	SD	24.25	0.1099	0.1819	0.1004	0.0024
	(n)	(5)	(5)	(5)	(5)	(5)

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
36710001	1	232.4	0.065	1.72	0.88	1.58	6.02	0.150
36710003	1	227.7	0.064	1.61	0.90	1.46	6.38	0.125
36710005	1	227.0	0.067	1.60	0.79	1.30	5.96	0.129
36710007	1	213.1	0.064	1.74	0.95	1.42	5.68	0.126
36710009	1	207.6	0.064	1.67	0.78	1.31	5.29	0.107
	Mean	221.56	0.0648	1.669	0.858	1.414	5.865	0.1274
	SD	10.62	0.0013	0.064	0.076	0.112	0.407	0.0153
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710021	2	212.2	0.054	1.68	0.76	1.37	5.49	0.116
36710023	2	228.7	0.061	1.63	0.98	1.48	6.40	0.134
36710025	2	215.6	0.059	1.67	0.76	1.22	5.72	0.090
36710029	2	227.7	0.062	1.60	0.83	1.44	6.16	0.116
	Mean	221.05	0.0590	1.642	0.832	1.377	5.942	0.1140
	SD	8.38	0.0036	0.037	0.107	0.116	0.410	0.0181
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36710031	3	231.7	0.058	1.63	0.79	1.52	6.84	0.112
36710033	3	207.3	0.079	1.71	0.83	1.41	6.80	0.139
36710035	3	213.8	0.079	1.73	0.86	1.45	6.69	0.111
36710037	3	203.2	0.064	1.67	0.87	1.38	6.16	0.131
36710039	3	208.1	0.056	1.65	0.83	1.40	6.10	0.100
	Mean	212.82	0.0672	1.679	0.835	1.432	6.518	0.1186
	SD	11.21	0.0112	0.042	0.032	0.058	0.359	0.0159
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710041	4	187.1	0.041	1.55	0.64	1.34	8.47	0.103
36710043	4	191.3	0.057	1.62	0.72	1.57	8.04	0.118
36710045	4	191.1	0.062	1.57	0.73	1.40	9.02	0.132
36710047	4	206.7	0.059	1.71	0.80	1.44	8.95	0.110
36710049	4	204.5	0.056	1.65	0.91	1.34	8.22	0.121
	Mean	196.14	0.0550	1.620	0.759	1.416	8.540	0.1168
	SD	8.83	0.0082	0.062	0.102	0.097	0.438	0.0110
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.1 - Absolute organ weights (g) - Final sacrifice - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Thyroid
36710001	1	232.4	0.780	0.436	0.014
36710003	1	227.7	0.654	0.359	0.017
36710005	1	227.0	0.587	0.417	0.015
36710007	1	213.1	0.785	0.356	0.010
36710009	1	207.6	0.683	0.309	0.017
	Mean	221.56	0.6978	0.3754	0.0146
	SD	10.62	0.0848	0.0511	0.0029
	(n)	(5)	(5)	(5)	(5)
36710021	2	212.2	0.534	0.422	0.015
36710023	2	228.7	0.705	0.377	0.014
36710025	2	215.6	0.468	0.459	0.017
36710029	2	227.7	0.716	0.305	0.018
	Mean	221.05	0.6058	0.3908	0.0160
	SD	8.38	0.1240	0.0663	0.0018
	(n)	(4)	(4)	(4)	(4)
36710031	3	231.7	0.559	0.393	0.015
36710033	3	207.3	0.489	0.336	0.012
36710035	3	213.8	0.497	0.390	0.016
36710037	3	203.2	0.601	0.512	0.017
36710039	3	208.1	0.533	0.407	0.014
	Mean	212.82	0.5358	0.4076	0.0148
	SD	11.21	0.0461	0.0643	0.0019
	(n)	(5)	(5)	(5)	(5)
36710041	4	187.1	0.380	0.323	0.016
36710043	4	191.3	0.456	0.316	0.016
36710045	4	191.1	0.426	0.350	0.013
36710047	4	206.7	0.463	0.290	0.015
36710049	4	204.5	0.512	0.326	0.014
	Mean	196.14	0.4474	0.3210	0.0148
	SD	8.83	0.0487	0.0215	0.0013
	(n)	(5)	(5)	(5)	(5)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.2 - Absolute organ weights (g) - Recovery sacrifice - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
36710012	1	378.3	0.065	1.75	1.395	1.24	2.28	9.59
36710014	1	349.5	0.044	1.76	1.130	1.17	2.00	8.38
36710016	1	382.3	0.052	1.84	1.217	1.29	2.39	10.57
36710018	1	340.8	0.044	1.80	1.124	1.20	1.97	8.33
36710020	1	372.4	0.042	1.72	1.129	1.18	2.13	9.08
	Mean	364.66	0.0494	1.773	1.1990	1.217	2.152	9.188
	SD	18.41	0.0095	0.045	0.1162	0.048	0.178	0.931
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710052	4	281.6	0.043	1.76	1.069	0.94	2.16	17.48
36710054	4	231.2	0.032	1.58	0.667	0.70	1.65	14.73
36710056	4	252.6	0.051	1.69	1.090	0.81	2.02	16.94
36710058	4	298.9	0.059	1.70	1.058	1.02	2.13	18.06
36710060	4	303.7	0.043	1.58	1.028	1.02	2.47	19.47
	Mean	273.60	0.0456	1.661	0.9824	0.897	2.089	17.336
	SD	31.02	0.0101	0.077	0.1777	0.139	0.295	1.733
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.2 - Absolute organ weights (g) - Recovery sacrifice - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus	Thyroid
36710012	1	378.3	0.990	3.743	0.476	0.021
36710014	1	349.5	0.753	3.598	0.433	0.017
36710016	1	382.3	0.990	3.621	0.470	0.025
36710018	1	340.8	0.785	3.939	0.553	0.019
36710020	1	372.4	0.801	3.641	0.443	0.017
	Mean	364.66	0.8638	3.7084	0.4750	0.0198
	SD	18.41	0.1165	0.1403	0.0472	0.0033
	(n)	(5)	(5)	(5)	(5)	(5)
36710052	4	281.6	0.575	3.368	0.346	0.021
36710054	4	231.2	0.529	2.939	0.086	0.017
36710056	4	252.6	0.543	3.649	0.315	0.030
36710058	4	298.9	0.670	3.479	0.492	0.016
36710060	4	303.7	0.613	3.692	0.334	0.026
	Mean	273.60	0.5860	3.4254	0.3146	0.0220
	SD	31.02	0.0570	0.3016	0.1459	0.0060
	(n)	(5)	(5)	(5)	(5)	(5)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.2 - Absolute organ weights (g) - Recovery sacrifice - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
36710011	1	233.5	0.059	1.69	0.79	1.35	5.61	0.118
36710013	1	215.1	0.050	1.69	0.76	1.35	5.43	0.122
36710015	1	219.2	0.069	1.72	0.86	1.38	5.15	0.106
36710017	1	222.4	0.052	1.68	0.82	1.40	5.43	0.115
36710019	1	222.4	0.046	1.53	0.81	1.31	5.45	0.120
	Mean	222.52	0.0552	1.660	0.808	1.359	5.413	0.1162
	SD	6.83	0.0090	0.074	0.037	0.034	0.167	0.0063
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710051	4	201.4	0.052	1.73	0.77	1.28	8.51	0.097
36710053	4	191.3	0.044	1.60	0.68	1.44	8.61	0.084
36710055	4	197.6	0.055	1.67	0.74	1.38	8.40	0.121
36710057	4	213.2	0.056	1.58	0.74	1.40	8.27	0.101
36710059	4	209.8	0.051	1.64	0.74	1.50	8.30	0.120
	Mean	202.66	0.0516	1.642	0.734	1.399	8.420	0.1046
	SD	8.92	0.0047	0.059	0.032	0.082	0.144	0.0158
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 10.2 - Absolute organ weights (g) - Recovery sacrifice - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Thyroid
36710011	1	233.5	0.689	0.616	0.025
36710013	1	215.1	0.634	0.330	0.011
36710015	1	219.2	0.571	0.322	0.019
36710017	1	222.4	0.634	0.327	0.015
36710019	1	222.4	0.511	0.354	0.021
	Mean	222.52	0.6078	0.3898	0.0182
	SD	6.83	0.0684	0.1270	0.0054
	(n)	(5)	(5)	(5)	(5)
36710051	4	201.4	0.515	0.336	0.017
36710053	4	191.3	0.510	0.308	0.016
36710055	4	197.6	0.549	0.286	0.026
36710057	4	213.2	0.506	0.363	0.015
36710059	4	209.8	0.559	0.398	0.024
	Mean	202.66	0.5278	0.3382	0.0196
	SD	8.92	0.0244	0.0443	0.0050
	(n)	(5)	(5)	(5)	(5)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11.1 - Relative organ weights° - Final sacrifice - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
36710002	1	335.6	0.016	0.53	0.315	0.37	0.62	2.63
36710004	1	361.2	0.012	0.49	0.289	0.33	0.61	2.80
36710006	1	348.9	0.018	0.51	0.323	0.37	0.64	2.80
36710008	1	340.7	0.012	0.54	0.330	0.39	0.60	2.61
36710010	1	348.3	0.012	0.54	0.316	0.32	0.62	2.49
	Mean	346.94	0.0140	0.521	0.3144	0.356	0.618	2.665
	SD	9.70	0.0029	0.022	0.0154	0.028	0.016	0.132
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710022	2	339.9	0.014	0.54	0.295	0.33	0.67	3.13
36710024	2	317.6	0.014	0.54	0.343	0.35	0.64	3.06
36710026	2	320.4	0.017	0.55	0.346	0.37	0.65	2.99
36710028	2	340.6	0.015	0.53	0.322	0.38	0.62	3.19
36710030	2	350.9	0.014	0.53	0.353	0.33	0.61	3.27
	Mean	333.88	0.0149	0.541	0.3318	0.350	0.641	3.130
	SD	14.30	0.0011	0.009	0.0235	0.022	0.023	0.109
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710032	3	343.8	0.011	0.54	0.291	0.34	0.65	4.24
36710034	3	346.7	0.014	0.52	0.316	0.38	0.72	4.13
36710036	3	354.8	0.020	0.52	0.349	0.35	0.73	4.21
36710038	3	329.1	0.013	0.55	0.321	0.35	0.68	3.90
36710040	3	331.5	0.014	0.55	0.332	0.37	0.67	4.43
	Mean	341.18	0.0146	0.535	0.3216	0.362	0.691	4.182
	SD	10.75	0.0033	0.015	0.0211	0.018	0.034	0.194
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710042	4	246.7	0.017	0.73	0.469	0.36	0.81	6.13
36710044	4	291.8	0.016	0.63	0.361	0.32	0.71	6.26
36710046	4	278.7	0.015	0.58	0.358	0.31	0.77	6.20
36710048	4	307.7	0.015	0.57	0.339	0.35	0.78	5.90
36710050	4	260.6	0.015	0.70	0.419	0.32	0.69	6.20
	Mean	277.10	0.0155	0.640	0.3890	0.331	0.753	6.138
	SD	24.25	0.0008	0.071	0.0538	0.022	0.051	0.141
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11.1 - Relative organ weights° - Final sacrifice - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus	Thyroid
36710002	1	335.6	0.268	1.217	0.147	0.008
36710004	1	361.2	0.239	0.989	0.153	0.006
36710006	1	348.9	0.288	1.093	0.140	0.008
36710008	1	340.7	0.240	1.064	0.183	0.007
36710010	1	348.3	0.244	1.031	0.134	0.007
	Mean	346.94	0.2559	1.0790	0.1515	0.0072
	SD	9.70	0.0214	0.0864	0.0193	0.0009
	(n)	(5)	(5)	(5)	(5)	(5)
36710022	2	339.9	0.265	1.081	0.192	0.008
36710024	2	317.6	0.220	1.136	0.171	0.009
36710026	2	320.4	0.214	1.181	0.135	0.008
36710028	2	340.6	0.231	1.152	0.195	0.008
36710030	2	350.9	0.266	1.111	0.132	0.006
	Mean	333.88	0.2392	1.1324	0.1649	0.0078
	SD	14.30	0.0246	0.0382	0.0303	0.0011
	(n)	(5)	(5)	(5)	(5)	(5)
36710032	3	343.8	0.209	1.009	0.161	0.008
36710034	3	346.7	0.256	1.104	0.142	0.008
36710036	3	354.8	0.271	1.109	0.179	0.008
36710038	3	329.1	0.227	1.205	0.146	0.008
36710040	3	331.5	0.220	1.096	0.171	0.008
	Mean	341.18	0.2367	1.1047	0.1599	0.0079
	SD	10.75	0.0258	0.0695	0.0156	0.0002
	(n)	(5)	(5)	(5)	(5)	(5)
36710042	4	246.7	0.177	1.534	0.075	0.010
36710044	4	291.8	0.242	1.260	0.106	0.009
36710046	4	278.7	0.179	1.298	0.143	0.008
36710048	4	307.7	0.199	1.207	0.136	0.009
36710050	4	260.6	0.186	1.272	0.091	0.009
	Mean	277.10	0.1968	1.3140	0.1102	0.0091
	SD	24.25	0.0269	0.1273	0.0289	0.0006
	(n)	(5)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11.1 - Relative organ weights° - Final sacrifice - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
36710001	1	232.4	0.028	0.74	0.38	0.68	2.59	0.065
36710003	1	227.7	0.028	0.71	0.39	0.64	2.80	0.055
36710005	1	227.0	0.030	0.70	0.35	0.57	2.62	0.057
36710007	1	213.1	0.030	0.82	0.45	0.67	2.67	0.059
36710009	1	207.6	0.031	0.80	0.37	0.63	2.55	0.052
	Mean	221.56	0.0293	0.755	0.388	0.638	2.646	0.0574
	SD	10.62	0.0012	0.053	0.037	0.040	0.097	0.0049
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710021	2	212.2	0.025	0.79	0.36	0.65	2.59	0.055
36710023	2	228.7	0.027	0.71	0.43	0.65	2.80	0.059
36710025	2	215.6	0.027	0.77	0.35	0.56	2.65	0.042
36710029	2	227.7	0.027	0.70	0.37	0.63	2.70	0.051
	Mean	221.05	0.0267	0.744	0.376	0.622	2.686	0.0515
	SD	8.38	0.0009	0.044	0.037	0.040	0.088	0.0072
	(n)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
36710031	3	231.7	0.025	0.70	0.34	0.66	2.95	0.048
36710033	3	207.3	0.038	0.83	0.40	0.68	3.28	0.067
36710035	3	213.8	0.037	0.81	0.40	0.68	3.13	0.052
36710037	3	203.2	0.031	0.82	0.43	0.68	3.03	0.064
36710039	3	208.1	0.027	0.79	0.40	0.67	2.93	0.048
	Mean	212.82	0.0317	0.791	0.394	0.673	3.065	0.0560
	SD	11.21	0.0058	0.051	0.033	0.009	0.143	0.0091
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710041	4	187.1	0.022	0.83	0.34	0.71	4.53	0.055
36710043	4	191.3	0.030	0.84	0.38	0.82	4.20	0.062
36710045	4	191.1	0.032	0.82	0.38	0.73	4.72	0.069
36710047	4	206.7	0.029	0.83	0.38	0.70	4.33	0.053
36710049	4	204.5	0.027	0.81	0.44	0.65	4.02	0.059
	Mean	196.14	0.0280	0.826	0.386	0.723	4.360	0.0596
	SD	8.83	0.0039	0.013	0.038	0.062	0.275	0.0062
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11.1 - Relative organ weights° - Final sacrifice - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Thyroid
36710001	1	232.4	0.336	0.188	0.006
36710003	1	227.7	0.287	0.158	0.007
36710005	1	227.0	0.259	0.184	0.007
36710007	1	213.1	0.368	0.167	0.005
36710009	1	207.6	0.329	0.149	0.008
	Mean	221.56	0.3158	0.1690	0.0066
	SD	10.62	0.0431	0.0166	0.0013
	(n)	(5)	(5)	(5)	(5)
36710021	2	212.2	0.252	0.199	0.007
36710023	2	228.7	0.308	0.165	0.006
36710025	2	215.6	0.217	0.213	0.008
36710029	2	227.7	0.314	0.134	0.008
	Mean	221.05	0.2729	0.1776	0.0072
	SD	8.38	0.0467	0.0354	0.0008
	(n)	(4)	(4)	(4)	(4)
36710031	3	231.7	0.241	0.170	0.006
36710033	3	207.3	0.236	0.162	0.006
36710035	3	213.8	0.232	0.182	0.007
36710037	3	203.2	0.296	0.252	0.008
36710039	3	208.1	0.256	0.196	0.007
	Mean	212.82	0.2523	0.1923	0.0070
	SD	11.21	0.0259	0.0357	0.0010
	(n)	(5)	(5)	(5)	(5)
36710041	4	187.1	0.203	0.173	0.009
36710043	4	191.3	0.238	0.165	0.008
36710045	4	191.1	0.223	0.183	0.007
36710047	4	206.7	0.224	0.140	0.007
36710049	4	204.5	0.250	0.159	0.007
	Mean	196.14	0.2278	0.1641	0.0076
	SD	8.83	0.0178	0.0160	0.0008
	(n)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11.2 - Relative organ weights° - Recovery sacrifice - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Epididymides	Heart	Kidneys	Liver
36710012	1	378.3	0.017	0.46	0.369	0.33	0.60	2.53
36710014	1	349.5	0.013	0.50	0.323	0.33	0.57	2.40
36710016	1	382.3	0.014	0.48	0.318	0.34	0.62	2.76
36710018	1	340.8	0.013	0.53	0.330	0.35	0.58	2.44
36710020	1	372.4	0.011	0.46	0.303	0.32	0.57	2.44
	Mean	364.66	0.0135	0.487	0.3287	0.334	0.590	2.515
	SD	18.41	0.0022	0.027	0.0245	0.013	0.023	0.148
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710052	4	281.6	0.015	0.63	0.380	0.33	0.77	6.21
36710054	4	231.2	0.014	0.68	0.288	0.30	0.72	6.37
36710056	4	252.6	0.020	0.67	0.432	0.32	0.80	6.71
36710058	4	298.9	0.020	0.57	0.354	0.34	0.71	6.04
36710060	4	303.7	0.014	0.52	0.338	0.33	0.81	6.41
	Mean	273.60	0.0166	0.613	0.3584	0.326	0.762	6.348
	SD	31.02	0.0031	0.068	0.0527	0.015	0.047	0.248
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11.2 - Relative organ weights° - Recovery sacrifice - Individual data

STUDY NO.: [redacted]

MALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Testes	Thymus	Thyroid
36710012	1	378.3	0.262	0.989	0.126	0.006
36710014	1	349.5	0.215	1.029	0.124	0.005
36710016	1	382.3	0.259	0.947	0.123	0.007
36710018	1	340.8	0.230	1.156	0.162	0.006
36710020	1	372.4	0.215	0.978	0.119	0.005
	Mean	364.66	0.2363	1.0199	0.1308	0.0054
	SD	18.41	0.0228	0.0815	0.0178	0.0008
	(n)	(5)	(5)	(5)	(5)	(5)
36710052	4	281.6	0.204	1.196	0.123	0.007
36710054	4	231.2	0.229	1.271	0.037	0.007
36710056	4	252.6	0.215	1.445	0.125	0.012
36710058	4	298.9	0.224	1.164	0.165	0.005
36710060	4	303.7	0.202	1.216	0.110	0.009
	Mean	273.60	0.2148	1.2583	0.1119	0.0081
	SD	31.02	0.0119	0.1112	0.0465	0.0024
	(n)	(5)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11.2 - Relative organ weights° - Recovery sacrifice - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	Terminal B.W. (g)	Adrenals	Brain	Heart	Kidneys	Liver	Ovaries
36710011	1	233.5	0.025	0.72	0.34	0.58	2.40	0.051
36710013	1	215.1	0.023	0.78	0.35	0.63	2.52	0.057
36710015	1	219.2	0.031	0.78	0.39	0.63	2.35	0.048
36710017	1	222.4	0.023	0.76	0.37	0.63	2.44	0.052
36710019	1	222.4	0.021	0.69	0.36	0.59	2.45	0.054
	Mean	222.52	0.0248	0.746	0.363	0.611	2.433	0.0523
	SD	6.83	0.0041	0.041	0.020	0.024	0.065	0.0032
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
36710051	4	201.4	0.026	0.86	0.38	0.64	4.23	0.048
36710053	4	191.3	0.023	0.83	0.36	0.75	4.50	0.044
36710055	4	197.6	0.028	0.84	0.38	0.70	4.25	0.061
36710057	4	213.2	0.026	0.74	0.35	0.66	3.88	0.047
36710059	4	209.8	0.024	0.78	0.35	0.72	3.95	0.057
	Mean	202.66	0.0254	0.812	0.363	0.691	4.163	0.0516
	SD	8.92	0.0019	0.049	0.015	0.046	0.250	0.0073
	(n)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 11.2 - Relative organ weights° - Recovery sacrifice - Individual data

STUDY NO.: [redacted]

FEMALES

Animal Number	Group	Terminal B.W. (g)	Spleen	Thymus	Thyroid
36710011	1	233.5	0.295	0.264	0.011
36710013	1	215.1	0.295	0.153	0.005
36710015	1	219.2	0.260	0.147	0.009
36710017	1	222.4	0.285	0.147	0.007
36710019	1	222.4	0.230	0.159	0.009
	Mean	222.52	0.2730	0.1741	0.0081
	SD	6.83	0.0280	0.0504	0.0022
	(n)	(5)	(5)	(5)	(5)
36710051	4	201.4	0.256	0.167	0.008
36710053	4	191.3	0.267	0.161	0.008
36710055	4	197.6	0.278	0.145	0.013
36710057	4	213.2	0.237	0.170	0.007
36710059	4	209.8	0.266	0.190	0.011
	Mean	202.66	0.2608	0.1665	0.0097
	SD	8.92	0.0153	0.0163	0.0025
	(n)	(5)	(5)	(5)	(5)

° = expressed as % organ to body weight ratio

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710002 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.

Whole animal . . . No abnormalities detected

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Heart	Ileum	Jejunum
Kidneys	Lungs	Mesenteric nodes	Parathyroid gl.
Pituitary	Prostate	Rectum	Sciatic nerve
Seminal vesicles	Spinal cord	Spleen	Stomach
Testes	Thymus	Thyroid	Trachea
Urinary bladder			

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710004 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Focal, Slight, Unilateral.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial. PERIBRONCHIAL LYMPHOID HYPERPLASIA, Slight.
Prostate		MIXED INFLAMMATORY CELL INFILTRATION, Multifocal, Mild.
Whole animal	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Heart	Ileum	Jejunum
Mesenteric nodes	Parathyroid gl.	Pituitary	Rectum
Sciatic nerve	Seminal vesicles	Spinal cord	Spleen
Stomach	Testes	Thymus	Thyroid
Trachea	Urinary bladder		

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710006 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Heart		CHRONIC INFLAMMATION, Focal, Slight, Myocardial.
Kidneys		NEPHROPATHY, Focal, Slight, Unilateral. INFLAMMATORY CELL INFILTRATION, Focal, Slight, Unilateral.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs	Abnormal area(s), Dark	INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial. ALVEOLAR HAEMORRHAGE, Focal, Slight.
Prostate		MIXED INFLAMMATORY CELL INFILTRATION, Multifocal, Mild.
Thyroid		THYRO-GLOSSAL DUCT REMNANT, Present.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain	
Caecum	Cervical nodes	Colon	Duodenum	
Epididymides	Ileum	Jejunum	Mesenteric nodes	
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve	
Seminal vesicles	Spinal cord	Spleen	Stomach	
Testes	Thymus	Trachea	Urinary bladder	

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710008 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Multifocal, Slight, Bilateral.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Mild. ALVEOLAR HAEMORRHAGE, Focal, Slight.
Parathyroid gl.		Tissue is missing.
Whole animal	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Heart	Ileum	Jejunum
Mesenteric nodes	Pituitary	Prostate	Rectum
Sciatic nerve	Seminal vesicles	Spinal cord	Spleen
Stomach	Testes	Thymus	Thyroid
Trachea	Urinary bladder		

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710010 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Jejunum	Abnormal contents, White, Mucoid	Tissue is unremarkable.
Kidneys		NEPHROPATHY, Focal, Slight, Unilateral.
Liver	Abnormal area(s), Multiple, Dark, Pinpoint	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial. PERIBRONCHIAL LYMPHOID HYPERPLASIA, Slight.
Parathyroid gl.		Tissue is missing.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain	
Caecum	Cervical nodes	Colon	Duodenum	
Epididymides	Heart	Ileum	Mesenteric nodes	
Pituitary	Prostate	Rectum	Sciatic nerve	
Seminal vesicles	Spinal cord	Spleen	Stomach	
Testes	Thymus	Thyroid	Trachea	
Urinary bladder				

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710012 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver	Abnormal size, Small	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial. VASCULAR MINERALIZATION, Focal, Present. FRAGMENT/S OF BONE, Focal, Present.
Spleen	Abnormal shape, Swollen	Tissue not examined microscopically.

The following tissues are normal microscopically: Thymus

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710014 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Ileum	Abnormal contents, Yellow, Mucoid	Tissue not examined microscopically.
Jejunum	Abnormal contents, Yellow, Mucoid	Tissue not examined microscopically.
Liver	Abnormal size, Small	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.

The following tissues are normal microscopically: Lungs Thymus

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710016 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial. VASCULAR MINERALIZATION, Focal, Present.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710018 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes	Abnormal size, Enlarged/ up to 7x5x3mm	Tissue not examined microscopically.
Liver	Abnormal size, Small	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		VASCULAR MINERALIZATION, Multifocal, Present.

The following tissues are normal microscopically: Thymus

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710020 Sex: Male Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight.

Whole animal . . . No abnormalities detected

The following tissues are normal microscopically: Lungs Thymus

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710022 Sex: Male Group: 2 Dose level: 0.3 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Mild, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		VASCULAR MINERALIZATION, Focal, Present.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710024 Sex: Male Group: 2 Dose level: 0.3 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight. HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular, Mid-zonal.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710026 Sex: Male Group: 2 Dose level: 0.3 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular, Mid-zonal.
Thymus	Abnormal area(s), Multiple, Red, Pinpoint/ left lobe	Tissue is unremarkable.

The following tissues are normal microscopically: Lungs

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710028 Sex: Male Group: 2 Dose level: 0.3 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight. HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular, Mid-zonal.
Lungs		VASCULAR MINERALIZATION, Focal, Present.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710030 Sex: Male Group: 2 Dose level: 0.3 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight. HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular, Mid-zonal.
Tail	Abnormal area(s), Multiple, Scab(s)/ up to 1x1mm	SCAB/S, Present. CHRONIC INFLAMMATION, Focal, Mild.

The following tissues are normal microscopically: Lungs Thymus

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710032 Sex: Male Group: 3 Dose level: 0.8 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys	Abnormal area(s), Two, Pale/ up to 2xmm, right	NEPHROPATHY, Multifocal, Slight, Unilateral.
Liver	Abnormal area(s), Multiple, Dark, Pinpoint	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular, Mid-zonal.

The following tissues are normal microscopically: Lungs Thymus

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710034 Sex: Male Group: 3 Dose level: 0.8 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver	Abnormal colour, Pale	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight. HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular, Mid-zonal. HEPATOCYTIC NECROSIS, Focal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.

The following tissues are normal microscopically: Thymus

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710036 Sex: Male Group: 3 Dose level: 0.8 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular, Mid-zonal.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial. VASCULAR MINERALIZATION, Focal, Present.
Spleen	Abnormal shape, Swollen	Tissue is unremarkable.
Thymus	Abnormal area(s), Multiple, Red, Pinpoint	Tissue is unremarkable.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710038 Sex: Male Group: 3 Dose level: 0.8 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight. HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular, Mid-zonal.
Lungs		ALVEOLAR HAEMORRHAGE, Multifocal, Slight. FRAGMENT/S OF BONE, Focal, Present.
Stomach	Abnormal area(s), Single, Dark/ 2x2mm, glandular region	Tissue is unremarkable.

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710040 Sex: Male Group: 3 Dose level: 0.8 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular, Mid-zonal.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710042 Sex: Male Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Focal, Slight, Unilateral.
Liver	Abnormal colour, Pale	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
	Abnormal shape, Swollen	BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Mild, Panlobular.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Prostate		MIXED INFLAMMATORY CELL INFILTRATION, Multifocal, Slight.
Seminal vesicles	Abnormal colour, Transparent	COLLOID DEPLETION, Slight.
Stomach	Abnormal size, Thickened/ glandular non glandular region	Tissue is unremarkable.
Thymus	Abnormal size, Small	ATROPHY, Slight.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Colon	Duodenum
Epididymides	Heart	Ileum	Jejunum
Mesenteric nodes	Parathyroid gl.	Pituitary	Rectum
Sciatic nerve	Spinal cord	Spleen	Testes
Thyroid	Trachea	Urinary bladder	

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710044 Sex: Male Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes		REACTIVE HYPERPLASIA, Mild.
Kidneys		NEPHROPATHY, Focal, Slight, Bilateral.
Liver	Abnormal area(s)/ multiple, dark, pinpoint; single, pale, firm, 17x15x7mm, c/s dark and pale, firm, right caudal caudate lobe	INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
	Abnormal size, Enlarged	BILE DUCT PROLIFERATION, Multifocal, Slight.
		HEPATOCYTIC HYPERTROPHY, Mild, Panlobular.
		HEPATOCYTIC NECROSIS, Multifocal, Marked, Right caudal caudate lobe.
Lungs		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
Parathyroid gl.		Tissue is missing.
Prostate		MIXED INFLAMMATORY CELL INFILTRATION, Multifocal, Slight.
Seminal vesicles		COLLOID DEPLETION, Slight.
Thymus		ATROPHY, Slight.
Urinary bladder		PROTEINACEOUS PLUG, Present.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710044 Sex: Male Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments			
The following tissues are normal microscopically:		Adrenals	Bronchi	Bone marrow	Brain
		Caecum	Colon	Duodenum	Epididymides
		Heart	Ileum	Jejunum	Mesenteric nodes
		Pituitary	Rectum	Sciatic nerve	Spinal cord
		Spleen	Stomach	Testes	Thyroid
		Trachea			

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710046 Sex: Male Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Interstitial. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular, Mid-zonal.
Lungs	Abnormal colour, Red	INFLAMMATORY CELL FOCI, Focal, Slight. AGGREGATIONS OF ALVEOLAR MACROPHAGES, Multifocal, Slight.
Pituitary		DEVELPMENTAL CYST(S), Present.
Prostate		MIXED INFLAMMATORY CELL INFILTRATION, Multifocal, Slight.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain	
Caecum	Cervical nodes	Colon	Duodenum	
Epididymides	Heart	Ileum	Jejunum	
Kidneys	Mesenteric nodes	Parathyroid gl.	Rectum	
Sciatic nerve	Seminal vesicles	Spinal cord	Spleen	
Stomach	Testes	Thymus	Thyroid	
Trachea	Urinary bladder			

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710048 Sex: Male Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes		REACTIVE HYPERPLASIA, Slight.
Kidneys		NEPHROPATHY, Focal, Slight, Unilateral.
Liver	Abnormal area(s), Single, Pale, Firm/ 4x3mm, right median lobe	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
	Abnormal colour, Pale	BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular, Mid-zonal.
		HEPATOCYTIC NECROSIS, Multifocal, Mild.
		CHRONIC INFLAMMATION, Focal, Moderate, with mineralization.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
Prostate		MIXED INFLAMMATORY CELL INFILTRATION, Multifocal, Slight.
Thymus		ATROPHY, Slight.
Urinary bladder		PROTEINACEOUS PLUG, Present.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710048 Sex: Male Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments			
The following tissues are normal microscopically:		Adrenals	Bronchi	Bone marrow	Brain
		Caecum	Colon	Duodenum	Epididymides
		Heart	Ileum	Jejunum	Mesenteric nodes
		Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
		Seminal vesicles	Spinal cord	Spleen	Stomach
		Testes	Thyroid	Trachea	

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710050 Sex: Male Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 29 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Adrenals	Abnormal size, Small/ 1mm diam left	Tissue is unremarkable.
Liver	Abnormal colour, Pale	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
	Abnormal shape, Swollen	BILE DUCT PROLIFERATION, Multifocal, Slight.
		HEPATOCYTIC HYPERTROPHY, Mild, Panlobular.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
		VASCULAR MINERALIZATION, Focal, Present.
		ALVEOLAR HAEMORRHAGE, Focal, Slight.
Parathyroid gl.		Tissue is missing.
Prostate		MIXED INFLAMMATORY CELL INFILTRATION, Multifocal, Slight.
Seminal vesicles	Abnormal colour, Transparent	COLLOID DEPLETION, Slight.
Thymus	Abnormal size, Small	Tissue is unremarkable.

The following tissues are normal microscopically:

Bronchi	Bone marrow	Brain	Caecum
Cervical nodes	Colon	Duodenum	Epididymides
Heart	Ileum	Jejunum	Kidneys
Mesenteric nodes	Pituitary	Rectum	Sciatic nerve
Spinal cord	Spleen	Stomach	Testes
Thyroid	Trachea	Urinary bladder	

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710052 Sex: Male Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Cervical nodes	Abnormal size, Single, Enlarged/ 10x8x2mm	Tissue not examined microscopically.
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Mild, Panlobular.
		HEPATOCYTIC NECROSIS, Focal, Mild.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		ALVEOLAR HAEMORRHAGE, Focal, Slight.
Seminal vesicles	Abnormal colour, Transparent	Tissue not examined microscopically.
Thymus	Abnormal size, Small	Tissue is unremarkable.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710054 Sex: Male Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys	Pelvic dilatation, Minimal/ right	Tissue not examined microscopically.
	Abnormal area(s), Single, Pale/ 4x2mm, right	
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
		HEPATOCYTIC HYPERTROPHY, Mild, Panlobular.
Mesenteric nodes	Abnormal colour, Two, Dark	Tissue not examined microscopically.
Seminal vesicles	Abnormal colour, Transparent	Tissue not examined microscopically.
Thymus	Abnormal size, Small	ATROPHY, Moderate.
Head	Abnormal area(s), Single, Scab(s)/ 7x4mm, muzzle, 9ABN SKIN 1)	

The following tissues are normal microscopically: Lungs

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710056 Sex: Male Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Mild, Panlobular.
Lungs		VASCULAR MINERALIZATION, Multifocal, Present.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710058 Sex: Male Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys	Pelvic dilatation, Minimal/ left	Tissue not examined microscopically.
	Abnormal area(s), Single, Pale/ 6x3mm, left	
Liver	Abnormal size, Enlarged	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
	Abnormal shape, Swollen	BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Mild, Panlobular.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		VASCULAR MINERALIZATION, Focal, Present.
Stomach	Abnormal contents, Yellow, Mucoid	Tissue not examined microscopically.

The following tissues are normal microscopically: Thymus

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710060 Sex: Male Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Mild, Panlobular.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial. AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight. VASCULAR MINERALIZATION, Focal, Present.
Head	Staining, Brown	

The following tissues are normal microscopically: Thymus

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710001 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver	Abnormal size, Small	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Thymus	Abnormal colour, Red/ left lobe	Tissue is unremarkable.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Kidneys	Mesenteric nodes	Ovaries	Oviducts
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
Spinal cord	Spleen	Stomach	Thyroid
Trachea	Urinary bladder	Uterus	

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710003 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys	Abnormal colour, Pale	Tissue is unremarkable.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Pituitary		DEVELPMENTAL CYST(S), Present.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Mesenteric nodes	Ovaries	Oviducts	Parathyroid gl.
Rectum	Sciatic nerve	Spinal cord	Spleen
Stomach	Thymus	Thyroid	Trachea
Urinary bladder	Uterus		

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710005 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Heart		CHRONIC INFLAMMATION, Focal, Slight, Myocardial.
Ileum	Abnormal contents, Yellow, Mucoid	Tissue is unremarkable.
Kidneys		NEPHROPATHY, Focal, Slight, Unilateral.
Liver		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Interstitial.
Uterus		GLANDULAR DILATATION, Focal, Slight.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Jejunum	Mesenteric nodes	Ovaries
Oviducts	Parathyroid gl.	Pituitary	Rectum
Sciatic nerve	Spinal cord	Spleen	Stomach
Thymus	Thyroid	Trachea	Urinary bladder

[redacted]

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710007 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		INFLAMMATORY CELL INFILTRATION, Focal, Slight, Unilateral.
Liver	Abnormal size, Small	INFLAMMATORY CELL FOCI, Multifocal, Mild, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		VASCULAR MINERALIZATION, Focal, Present.
Ovaries	Abnormal size, Enlarged/ up to 7x5x3mm	LUTEIN CYST, Unilateral, Present.
Spleen	Abnormal shape, Swollen	Tissue is unremarkable.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Mesenteric nodes	Oviducts	Parathyroid gl.	Pituitary
Rectum	Sciatic nerve	Spinal cord	Stomach
Thymus	Thyroid	Trachea	Urinary bladder
Uterus			

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710009 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Parathyroid gl.		Tissue is missing.
Stomach		INFLAMMATORY CELL INFILTRATION, Focal, Slight, Limiting ridge.
Whole animal	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Kidneys	Mesenteric nodes	Ovaries	Oviducts
Pituitary	Rectum	Sciatic nerve	Spinal cord
Spleen	Thymus	Thyroid	Trachea
Urinary bladder	Uterus		

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710011 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

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Tissue	Gross observations / Comments	Microscopic observations / Comments
Ileum	Abnormal contents, Yellow, Mucoid	Tissue not examined microscopically.
Jejunum	Abnormal contents, Yellow, Mucoid	Tissue not examined microscopically.
Liver	Abnormal size, Small	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.

The following tissues are normal microscopically: Lungs Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710013 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Jejunum	Abnormal contents, Yellow, Mucoid	Tissue not examined microscopically.
Liver	Abnormal size, Small	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Stomach	Abnormal contents, White, Granular	Tissue not examined microscopically.

The following tissues are normal microscopically: Lungs Thymus

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710015 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

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Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver	Abnormal size, Small	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
	Abnormal colour, Pale	BILE DUCT PROLIFERATION, Multifocal, Slight.
Skin	Staining, Brown/ neck	

The following tissues are normal microscopically: Lungs Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710017 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

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Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial. VASCULAR MINERALIZATION, Focal, Present.
Skin	Staining, Brown/ neck	

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710019 Sex: Female Group: 1 Dose level: 0.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

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Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710021 Sex: Female Group: 2 Dose level: 0.3 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight.
Lungs		VASCULAR MINERALIZATION, Focal, Present.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710023 Sex: Female Group: 2 Dose level: 0.3 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		ALVEOLAR HAEMORRHAGE, Focal, Slight.
Whole animal . . .	No abnormalities detected, Single	

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710025 Sex: Female Group: 2 Dose level: 0.3 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710027 Sex: Female Group: 2 Dose level: 0.3 mg/kg/day
Day of death: 23 Dosing phase Status: Found dead

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver	Abnormal area(s), Two, Ruptured/ up to 8x4mm, right, left median lobe	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		HAEMORRHAGE, Multifocal, Mild.
Lungs	Abnormal colour, Pale	INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		FRAGMENT/S OF BONE, Focal, Present.
Thymus	Abnormal colour, Red	CONGESTION/HAEMORRHAGE, Slight.
	Abnormal area(s), Multiple, Dark, Pinpoint/ right lobe	
Uterus	Abnormal size, Distended/ 5mm diam	HYDROMETRA, Bilateral, Slight.
	Abnormal contents, Clear, Fluid	
Abdominal cavity .	Abnormal contents, Dark red/ fluid and soft	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Kidneys	Mesenteric nodes	Ovaries	Oviducts
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
Spinal cord	Spleen	Stomach	Thyroid
Trachea	Urinary bladder		

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710029 Sex: Female Group: 2 Dose level: 0.3 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial. VASCULAR MINERALIZATION, Focal, Present.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710031 Sex: Female Group: 3 Dose level: 0.8 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically: Lungs Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710033 Sex: Female Group: 3 Dose level: 0.8 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Skin	Staining, Brown/ neck	
Head	Staining, Brown	

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710035 Sex: Female Group: 3 Dose level: 0.8 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Thymus	Abnormal colour, Red/ left lobe	Tissue is unremarkable.
Uterus	Abnormal size, Distended/ 4mm diam	GLANDULAR DILATATION, Multifocal, Slight.
	Abnormal contents, Clear, Fluid	HYDROMETRA, Bilateral, Mild.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710037 Sex: Female Group: 3 Dose level: 0.8 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Interstitial.
		ALVEOLAR HAEMORRHAGE, Multifocal, Mild.
Ovaries	Abnormal size, Enlarged/ up to 8x4x3mm	Tissue is unremarkable.
Spleen	Abnormal shape, Swollen	Tissue is unremarkable.
Thymus	Abnormal area(s), Multiple, Red, Pinpoint	Tissue is unremarkable.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710039 Sex: Female Group: 3 Dose level: 0.8 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight.
Lungs	Abnormal area(s), Multiple/ dark red up to 7x4mm, right lobes; red pinpoint left, right caudal lobes	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Interstitial. ALVEOLAR HAEMORRHAGE, Multifocal, Mild.

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710041 Sex: Female Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular, Mid-zonal.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Uterus		HYDROMETRA, Bilateral, Slight.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Kidneys	Mesenteric nodes	Ovaries	Oviducts
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
Spinal cord	Spleen	Stomach	Thymus
Thyroid	Trachea	Urinary bladder	

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710043 Sex: Female Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Interstitial. BILE DUCT PROLIFERATION, Multifocal, Slight. HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular, Mid-zonal.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial. AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
Parathyroid gl.		Tissue is missing.
Uterus		GLANDULAR DILATATION, Multifocal, Slight.
Skin	Staining, Brown/ neck	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Kidneys	Mesenteric nodes	Ovaries	Oviducts
Pituitary	Rectum	Sciatic nerve	Spinal cord
Spleen	Stomach	Thymus	Thyroid
Trachea	Urinary bladder		

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710045 Sex: Female Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Kidneys		NEPHROPATHY, Focal, Slight, Bilateral.
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular, Mid-zonal.
Lungs		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Mesenteric nodes	Ovaries	Oviducts	Parathyroid gl.
Pituitary	Rectum	Sciatic nerve	Spinal cord
Spleen	Stomach	Thymus	Thyroid
Trachea	Urinary bladder	Uterus	

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710047 Sex: Female Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver	Abnormal colour, Pale	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular, Mid-zonal.
Lungs		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Interstitial. ALVEOLAR HAEMORRHAGE, Multifocal, Mild.
Thymus		ATROPHY, Slight.
Uterus		GLANDULAR DILATATION, Multifocal, Slight. HYDROMETRA, Bilateral, Mild.

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Kidneys	Mesenteric nodes	Ovaries	Oviducts
Parathyroid gl.	Pituitary	Rectum	Sciatic nerve
Spinal cord	Spleen	Stomach	Thyroid
Trachea	Urinary bladder		

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710049 Sex: Female Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 30 Dosing phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Mild, Centrilobular, Mid-zonal.
Lungs		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Interstitial. ALVEOLAR HAEMORRHAGE, Multifocal, Slight.
Ovaries		LUTEIN CYST, Unilateral, Present.
Thyroid		THYRO-GLOSSAL DUCT REMNANT, Present.
Whole animal . . .	No abnormalities detected	

The following tissues are normal microscopically:

Adrenals	Bronchi	Bone marrow	Brain
Caecum	Cervical nodes	Cervix	Colon
Duodenum	Heart	Ileum	Jejunum
Kidneys	Mesenteric nodes	Oviducts	Parathyroid gl.
Pituitary	Rectum	Sciatic nerve	Spinal cord
Spleen	Stomach	Thymus	Trachea
Urinary bladder	Uterus		

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710051 Sex: Female Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight. HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular, Mid-zonal.
Thymus	Abnormal size, Small	Tissue is unremarkable.
Head	Staining, Brown	

The following tissues are normal microscopically: Lungs

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710053 Sex: Female Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Mild, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight. HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular, Mid-zonal.
Lungs		VASCULAR MINERALIZATION, Multifocal, Present.
Stomach	Abnormal contents, Yellow, Soft	Tissue not examined microscopically.

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710055 Sex: Female Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Jejunum	Abnormal contents, Yellow, Mucoid	Tissue not examined microscopically.
Liver	Abnormal area(s), Multiple, Dark, Pinpoint	INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Focal, Slight. HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular, Mid-zonal.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.

The following tissues are normal microscopically: Thymus

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710057 Sex: Female Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular.
		BILE DUCT PROLIFERATION, Focal, Slight.
		HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular, Mid-zonal.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
		AGGREGATIONS OF ALVEOLAR MACROPHAGES, Focal, Slight.
		VASCULAR MINERALIZATION, Focal, Present.
		ALVEOLAR HAEMORRHAGE, Focal, Slight.
Stomach	Abnormal contents, Yellow, Mucoid	Tissue not examined microscopically.
Thymus	Abnormal area(s), Multiple, Red/ up to 2x2mm	Tissue is unremarkable.

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

APPENDIX 12 - Macroscopic and microscopic observations - Individual data

STUDY NO.: [redacted]

Animal: 36710059 Sex: Female Group: 4 Dose level: 2.0 mg/kg/day
Day of death: 15 Recovery phase Status: Final phase sacrifice

Tissue	Gross observations / Comments	Microscopic observations / Comments
Liver		INFLAMMATORY CELL FOCI, Multifocal, Slight, Perivascular, Intralobular. BILE DUCT PROLIFERATION, Multifocal, Slight. HEPATOCYTIC HYPERTROPHY, Slight, Centrilobular, Mid-zonal.
Lungs		INFLAMMATORY CELL FOCI, Focal, Slight, Perivascular, Interstitial.
Thymus	Abnormal area(s), Multiple, Red, Pinpoint	Tissue is unremarkable.
Uterus	Abnormal size, Distended/ 5mm diam	Tissue not examined microscopically.
Uterus	Abnormal contents, Clear, Fluid	
Head	Staining, Brown	

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM I - Computer abbreviations and symbols

STUDY NO.: [redacted]

Abbreviations	Parameter names	Units
HCT	HAEMATOCRIT	%
RBC	RED BLOOD CELL COUNT	10^12/l
HGB	HAEMOGLOBIN	g/dl
MCV	MEAN RED BLOOD CELL VOLUME	fl
MCH	MEAN CORPUSCULAR HAEMOGLOBIN	pg
MCHC	MEAN CORPUSCULAR HAEMOGLOBIN CONCENTRATION	g/dl
PLT	PLATELETS	10^9/l
WBC	WHITE BLOOD CELL COUNT	10^9/l
NEU	NEUTROPHILS	%
LYM	LYMPHOCYTES	%
MON	MONOCYTES	%
EOS	EOSINOPHILS	%
BAS	BASOPHILS	%
LUC	LARGE UNSTAINED CELLS	%
PT	PROTHROMBIN TIME	sec
AP	ALKALINE PHOSPHATASE	U/l
ALT	ALANINE AMINOTRANSFERASE	U/l
AST	ASPARTATE AMINOTRANSFERASE	U/l
GGT	GAMMAGLUTAMYLTRANSFERASE	U/l
GLU	GLUCOSE	mg/dl
BILT	TOTAL BILIRUBIN	mg/dl
CHOL	TOTAL CHOLESTEROL	mg/dl
PROT	TOTAL PROTEIN	g/dl
NA	SODIUM	mmol/l
K	POTASSIUM	mmol/l
CA	CALCIUM	mmol/l
CL	CHLORIDE	mmol/l
UREA	UREA	mg/dl
CREA	CREATININE	mg/dl
VOL	URINE VOLUME (OVERNIGHT)	ml
SG	SPECIFIC GRAVITY	
PRO	PROTEIN	mg/dl
BLD	HAEMOGLOBIN	mg/dl
KET	KETONES	mg/dl
BIL	BILIRUBIN	mg/dl
URO	UROBILINOGEN	mg/dl
TRI	TRIGLYCERIDES	mg/dl
ALB	ALBUMIN	g/dl
GLO	GLOBULIN	g/dl
AGR	ALBUMIN/GLOBULIN RATIO	

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM I - Computer abbreviations and symbols

STUDY NO.: [redacted]

Abbreviations	Parameter names	Units/Key
EPI	EPITHELIAL CELLS	0 = no cells or crystals 1 = few cells or crystals in some fields 2 = few cells or crystals in all fields 3 = many cells or crystals in all fields
LEU	LEUCOCYTES	
ERY	ERYTHROCYTES	
CRY	CRYSTALS	
SPE	SPERMATOZOA	
ABN	ABNORMAL COMPONENTS	
APP	URINE APPEARANCE	0 = normal 1 = turbid
RED	REDUCING SUBSTANCES	0 = 0.0 - 2.5 g/l 1 = 2.5 - 7.5 g/l 2 = 7.5 - 10.0 g/l 3 = 10.0 - 20.0 g/l
Ctls	Control	
SD	Standard deviation	
Cervical nodes	Cervical lymph nodes	
Mesenteric nodes	Mesenteric lymph nodes	
gl	Glands	

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM II - Abbreviations of neurotoxicity tests

STUDY NO.: [redacted]

STIMULUS REACTIVITY		
APPR	APPROACH RESPONSE	1) no reaction 2) rat slowly approaches and sniffs or turns away 3) rat freezes, actual muscle contractions 4) more energetic response than 2) or 3) 5) exaggerated reaction - jumps, bites, or attacks
TOUC	TOUCH RESPONSE	1) no response 2) rat may slowly turn or walk away, or vocalizations with little or no movement 3) rat freezes, actual muscle contractions 4) more energetic response than 2) or 3) 5) exaggerated reaction - jumps, bites, or attacks
CLIK	CLIKER RESPONSE	1) no reaction 2) slight reaction, some evidence that noise was heard 3) rat freezes, actual muscle contractions 4) more energetic response than 2) or 3) 5) exaggerated reaction - jumps, bites, or attacks
TAIL	TAIL PINCH RESPONSE	1) no reaction 2) rat may turn or walk forward, or vocalizations with little or no movement 3) rat freezes, actual muscle contractions 4) more energetic response than 2) or 3) 5) exaggerated response - jumps, bites, or attacks
COUN	COUNT	The number of times the animal crosses the beam of the photoelectric cell.
BW		Body weight

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM II - Abbreviations of neurotoxicity tests

STUDY NO.: [redacted]

Abbreviations	**Parameter names**	**Key**
PUPI	PUPIL RESPONSE	constriction of the pupil is noted with "+" and "-" indicates lack of response
RIGH	RIGHTING REFLEX	1) normal, rat lands on feet 2) slightly uncoordinated 3) lands on side 4) lands on back
GRI1/2/M	GRIP STRENGTH 1/2/MEAN	two readings (GRI 1 and GRI 2) are taken and averaged. Forelimb strength is evaluated by assessing the time (seconds) the animal grips on a horizontal bar
LAN1/2/M	LANDING FOOT SPLAY 1/2/MEAN	two readings are taken and averaged. Measurements of distance between ink blots (cm)

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM III - Analytical method and validation report for formulation analysis and formulation analysis results

STUDY NO.: [redacted]

WARNING AND SAFETY PRECAUTIONS

SAFETY

Organic solvents - all organic solvents must be treated as potentially hazardous and all procedures using them must be performed in a fume cupboard.

[redacted]

Appropriate eye protection, impervious gloves and lab coat should be worn.

This method requires the use of corrosive and toxic reagents. It is the responsibility of the analyst to perform the method consistent with safe laboratory practices. The analyst should wear eye protection, impervious gloves, and a lab coat when preparing standards and processing samples. Caution statements have been included in the method giving specific guidance to certain procedural steps. Detailed hazard information should be obtained from the current MSDS available from the manufacturer of the solvent or reagent.

FIRST AID

Solvents, acids and alkalis in contact with skin - wash with copious amounts of cold water. Splashes in the eye - irrigate with water and seek medical attention immediately.

Cuts - seek assistance of first aide immediately.

Burns and frostbite - run affected part under cold water (burns) or tepid water (frostbite) for 10 minutes and seek medical attention.

INTRODUCTION

[redacted] is a product developed by the Sponsor. [redacted] is a [redacted]

1. SCOPE

This method of analysis describes the analysis of [redacted] in water.

2. FIELD OF APPLICATION

The method is described to be used for formulated product in water. The range of application is from 0.03mg/mL to 0.2mg/mL).

3. **REFERENCES**

ISO Standard 78/2-1982 Layout for standards - Part 2: Standard for Chemical Analysis

4. **DEFINITIONS**

[redacted] content is taken to mean the amount of [redacted] in the formulation determined according to the described method and expressed as mg of analyte per ml test sample.

5. **PRINCIPLE**

The method essentially consists of five steps:

- Sampling
- Evaporation
- Esterification
- Extraction with 2,2,4 Trimethylpentane (Isooctane)
- GC/FID

6. **REACTIONS**

7. **REAGENTS AND MATERIALS**

Note: The reagents (and equipment) for which examples of their sources are quoted are known to be satisfactory, nevertheless reagents and equipment from other sources may be equally suitable. All the reagents must be of analytical grade or better.

7.1 **Chemicals**

2,2,4 Trimethylpentane (Isooctane) (Aldrich 360597)

[redacted] reference standard batch 90409/86-I

Phenantrene Internal Standard. (Fluka 77470) batch 381400/1 10900

N-Hexane (Carlo Erba 46963)

Methanol (J.T. Baker 8402)

Water (produced by Easypure)

Ammonium hydroxide 32% (Merck 5426)

Sulphuric acid 98% (J.T. Baker 6163-1)

7.2 **Solutions**

Internal Standard:
About 8 mg are transferred into a 10mL volumetric flask and dissolved with N-Hexane obtaining a 800µg/mL solution. 1mL of this solution is transferred into a 10 ml volumetric flask and dissolved with Isooctane obtaining an 80µg/mL solution.

1% (W/W) H_2SO_4 in Methanol:
In a 250mL glass flask weigh 160g of Methanol and slowly add 1.7g of Sulphuric acid.

7.3 Standard solutions

7.3.1 [redacted] Stock A:

Due to a difficulty in weighing the substance, about 30 mg of analytical standard are transferred into 10 ml volumetric flask and dissolved with Methanol. An adequate dilution was made to obtain a 2500µg/mL solution (Stock1).

7.3.2 [redacted] Std 1:

50µL of Stock1 are diluted in 4950µL of water into a glass vial.

7.3.3 [redacted] Std 2:

100µL of Stock1 are diluted in 4900µL of water into a glass vial.

7.3.4 [redacted] Std 3:

150µL of Stock1 are diluted in 4850µL of water into a glass vial.

7.3.5 [redacted] Low recovery (0.03mg/mL):

60µL of Stock1 are diluted in 4940µL of water into a glass vial.

7.3.6 [redacted] High recovery (0.2mg/mL):

400µL of Stock1 are diluted in 4600µL of water into a glass vial.
1250µL of this solution are added in 3750µL of water into a glass vial

8. APPARATUS

Analytical balance	Mettler AT 261 Delta range
GC	Fisons Trace GC
Detector	Flame ionisation detector
Software	Empower Pro Build N°1154
Printer	HP Laser Jet 4050 Series PCL6
Column	ZB-1 30m x 0.32mm ID x 0.5µm FT
GC siring for OC	Hamilton 80351
GC microvials	
Pasteur pipettes	
Volumetric pipettes	
Common glassware	
Evaporator	Reacti Therm III Pierce
Air circulation oven	

9. SAMPLING AND SAMPLES

Nature of the Sample; Samples shall be such as to enable the detection of substance in the relevant formulations.

Size of Sample; The size of the sample must be large enough to allow the method to be carried out and to allow repeated analysis where required.

The samples must be taken and packed in such a way as to allow proper identification in the laboratory.

The method of packing, preservation and transport must maintain the integrity of the sample and not prejudice the results of the examination. Samples for the analysis of [redacted] must be stored at room temperature.

10. PROCEDURE

10.1 Sampling

10.1.1 Calibration and recovery samples

Add 30µL of Ammonium hydroxide 32% to the sample. Evaporate the sample to dryness in the Reactitherm at about 60°C with a gentle stream of nitrogen.
Add to the sample 500µL of 1% (W/W) H_2SO_4 in Methanol and heat the vials for 16 hours in a 70°C air circulation oven.
Add, at room temperature, 250µL of Isooctane, 50µL of ISTD and 2mL of water. Allow a good phase separation and then draw the superior phase for the analyses in GC.

10.1.2 Blank and unknown samples.

Samples are taken as follows:

		Expected			
Step	Action	0mg/mL	0.03mg/mL	0.08mg/mL	0.2mg/mL
1	transfer	5mL	5mL	2.5mL	1.25mL
	dilute with water to			5mL	5mL

For other concentrations samples will be prepared with an appropriate dilution.

Transfer into GC vials.

10.1.3 GC

The following system is set up:

Column:	ZB-1 30 m x 0.32 mm ID x 0.5 µm FT
Carrier:	Helium (2mL/Min)
Hydrogen:	30mL/Min

Air:	120mL/Min
Detector:	Flame ionization detector (FID) 250°C
Injector	On column at room temperature
Injection volume:	1µl
Oven:	40°C ----- 8°C/Min ----→250°C (10Min.)
Retention Time:	12 minutes for [redacted] and 26.5 minutes for Phenantrene (ISTD)
Run time:	35 minutes

As a test of system suitability, inject 1µl of any of the Standard Curve Solutions and observe the retention time of the [redacted] peak. To be acceptable, the retention time of the [redacted] peak must fall in the range of 11 to 13 minutes. If the retention time of [redacted] falls outside the acceptable range for the system suitability standard solution, the mobile phase (Carrier) must be adjusted in the following ways. If the retention time of [redacted] is before 11 min. the mobile phase should be adjusted by increasing the carrier flow. Conversely, if the retention time of [redacted] is after 13 min. the mobile phase should be adjusted by decreasing the carrier flow.

The GC is calibrated using the chromatographic software which generates a linear calibration curve drawing the best fit of a line, to the amounts of [redacted] in µg/mL and the response factor peaks area (Std and Istd). The software uses linear fit formula. The result of the fitting is:

$y = A + B^* x$
where
B = Slope of the calibration curve
A= Intercept
y = Response factor
x = [redacted] amount in µg/mL

Unknown samples are injected after the GC calibration. Results of the [redacted] amount in µg/mL are obtained directly from the GC report. The result is calculated by the software as:

$x = (y-A) / B$

11. EXPRESSION OF RESULTS

[redacted] contents in matrix as µg/mL are obtained as follows:

$C = (x \bullet FD) / 1000$

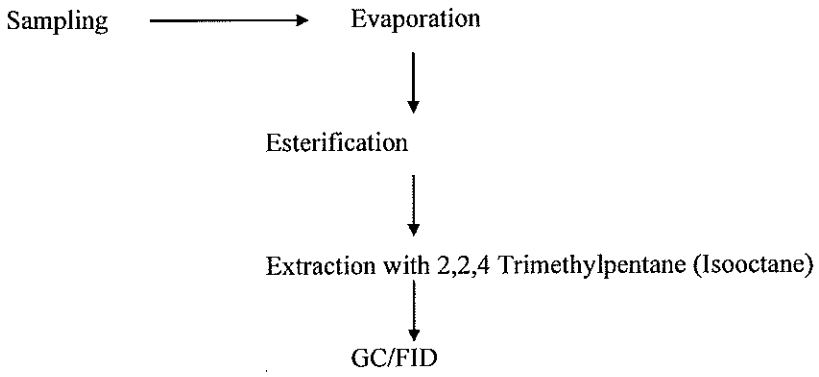
where:
C = content of [redacted] in water as µg/mL
x = [redacted] amount in µg/mL as read in the chromatogram result table
FD = Dilution Factor

12. **SPECIAL CASES**

13. **NOTES ON PROCEDURE**

14. **TEST REPORT**

15. **SCHEMATIC REPRESENTATION OF PROCEDURE**



16. **BIBLIOGRAPHY**

Analytical method [redacted]

17. **VALIDATION RESULTS**

17.1 **Linearity**

Calibration samples in triplicate at three levels ranging from 25µg/mL to 75µg/mL were processed as described in the analytical method. The following correlation was found:

Added ng/ml	Response (IS Analyte/ Analyte area)	Calculated Concentration (ng/mL)	Deviation %
25.16	0.308	27.512	-8.549
25.16	0.327	29.002	-13.246
25.16	0.287	25.773	-2.378
50.32	0.535	45.918	9.586
50.32	0.521	44.778	12.376
50.32	0.544	46.650	7.866
75.48	0.926	77.540	-2.656
75.48	0.953	79.738	-5.340
75.48	0.906	75.969	-0.644

Equation: Response = -0.031570 + 0.012348* [redacted] Conc.
r: 0.986227
Response type: area
Fit type: linear
Weighting: none

17.2 **Selectivity**

No interfering peaks were present at the [redacted] retention time.

17.3 **Accuracy and precision**

Sextuplicates at the following concentration were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
µg/mL	µg/mL	Mean (µg/mL)	%	CV %
30.192	30.974 30.47 30.968 30.528 31.079 30.828	30.81	102.04	0.82
201.28	201.76 193.536 207.764 201.532 199.9 202.056	201.1	99.91	2.27

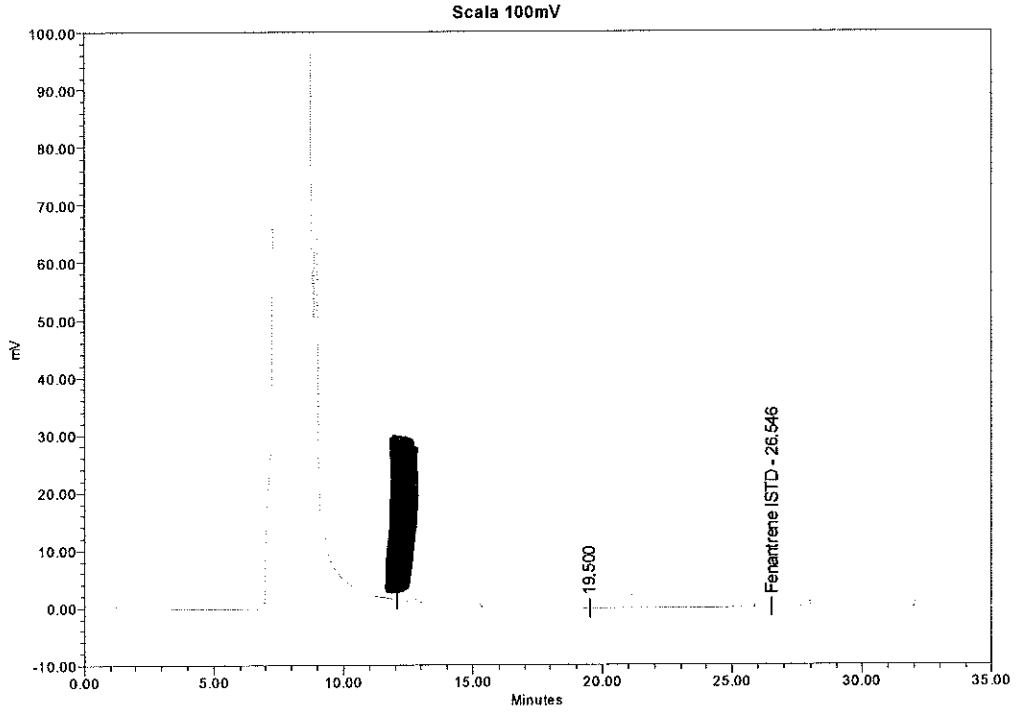
Chromatogram of a blank samples

Sample Information

Project Name: [redacted]
SampleName: Isottano
Sample Type: Unknown
Vial: 1
Injection: 1
Injection Volume: 1.00 ul
Channel: SATIN
Run Time: 35.0 Minutes
Label:

Acq Method Set: [redacted]
Date Acquired: 22-Mar-05 08:11:42
Date Processed: 22-Mar-05 13:30:35
Processing Method: [redacted]
System Name: TraceGC
Sample Set Name: [redacted] Seduta 1 Validazione
System Node: Capi
Acquired By: Riccir

Instrument Method Id 5271 Report Method ID 5540 Processing Method Id 5502 Channel Id 5430



Peak Results

	Name	RT	Area	Height	Amount	Units
1	[redacted]	12.075				
2		19.500	487	-74		
3	Fenantrene ISTD	26.546				

Calibration Curve

	Name	Date Calibrated	A	B	R	R^2	Processing Method
1	[redacted]	22-Mar-05 13:30:05	-3.261100e-002	1.227606e-002	0.984386	0.969015	[redacted]
2	Fenantrene ISTD	22-Mar-05 13:30:05	0.000000e+000	4.945317e+004	1.000000	1.000000	[redacted]

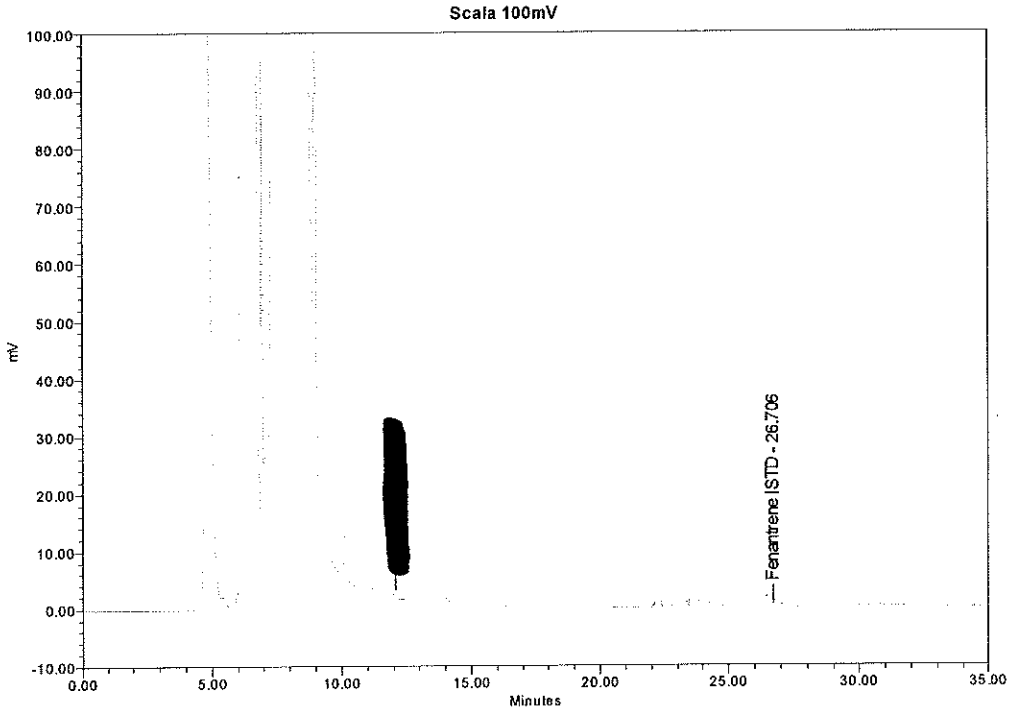
Chromatogram of a standard solution at approximately a 50 µg/mL

Sample Information

Project Name: [redacted]
SampleName: Std 2 50µg/mL
Sample Type: Standard
Vial: 4
Injection: 1
Injection Volume: 1.00 ul
Channel: SATIN
Run Time: 35.0 Minutes
Label: Linearità

Acq Method Set: [redacted]
Date Acquired: 22-Mar-05 10:25:38
Date Processed: 22-Mar-05 13:28:36
Processing Method: [redacted]
System Name: TraceGC
Sample Set Name: [redacted] Seduta 1 Validazione
System Node: Capi
Acquired By: Riccir

Instrument Method Id 5271 Report Method ID 5540 Processing Method Id 5502 Channel Id 5441



Peak Results

	Name	RT	Area	Height	Amount	Units
1	[redacted]	12.071	25389	3367	50.320	µg/mL
2	Fenantrene ISTD	26.706	48699	1962	1.000	µg/mL

Calibration Curve

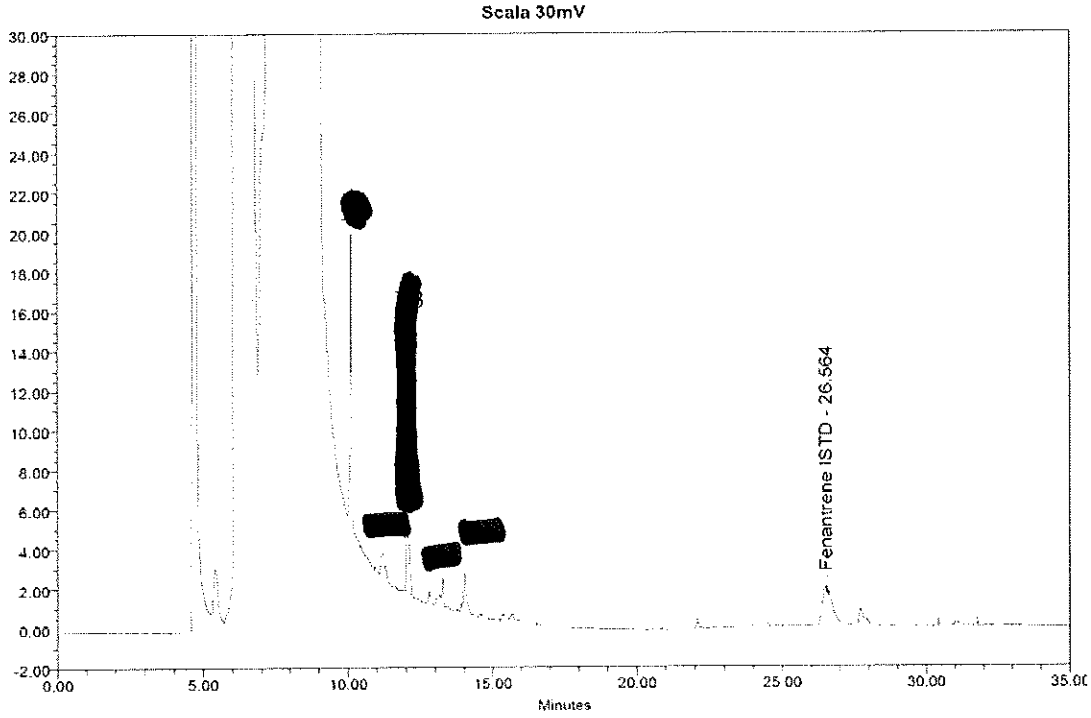
	Name	Date Calibrated	A	B	R	R^2	Processing Method
1	[redacted]	22-Mar-05 13:30:05	-3.261100e-002	1.227606e-002	0.984386	0.969015	[redacted]
2	Fenantrene ISTD	22-Mar-05 13:30:05	0.000000e+000	4.945317e+004	1.000000	1.000000	

Expanded Chromatogram on Standard Solution

Sample Information

Project Name:	[redacted]	Acq Method Set:	[redacted]
SampleName:	Std 2B 50µg/mL	Date Acquired:	24-Mar-05 11.34.06
Sample Type:	Standard	Date Processed:	24-Mar-05 13.58.33
Vial:	5	Processing Method	[redacted]
Injection:	1	System Name:	TraceGC
Injection Volume:	1.00 ul	Sample Set Name:	[redacted] Seduta 2
Channel:	SATIN	System Node:	Capi
Run Time:	35.0 Minutes	Acquired By:	Riccir
Label:	Controllo_Pesata		

Instrument Method Id 5271 Report Method ID 6454 Processing Method Id 5667 Channel Id 5650



Peak Results

	Name	RT	Area	Height	Amount	Units
1	[redacted]	12.087	32779	4665	49.968	µg/mL
2	Fenantrene ISTD	26.564	48567	1997	1.000	µg/mL

Calibration Curve

	Name	Date Calibrated	A	B	R	R^2
1	[redacted]	24-Mar-05 13.58.45	0.000000e+000	1.347710e-002	0.315746	0.099696
2	Fenantrene ISTD	24-Mar-05 13.58.45	0.000000e+000	4.648375e+004	1.000000	1.000000

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Formulation analysis - Pre-treatment - Content check

STUDY NO.: [redacted]

Group	Sex	Intended Concentration mg/ml	Found Concentration mg/ml	Recovery %	Recovery Limits %
1	M-F	0	0	-	-
2	M-F	0.03	0.0305	101.67	95 -105
3	M-F	0.08	0.0784	98.00	95 -105
4-5	M-F	0.2	0.1988	99.38	95 -105

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Formulation analysis - Stability 6 days at room temperature - Content check

STUDY NO.: [redacted]

Group	Sex	Intended Concentration mg/ml	Found Concentration mg/ml	Recovery %	Recovery Limits %
2	M-F	0.03	0.02978	99.27	95 -105
4-5	M-F	0.2	0.1928	96.42	95 -105

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Formulation analysis - Day 1 of treatment - Content check

STUDY NO.: [redacted]

Group	Sex	Intended Concentration mg/ml	Found Concentration mg/ml	Recovery %	Recovery Limits %
1	M-F	0	0	-	-
2	M-F	0.03	0.03061	102.04	95 -105
3	M-F	0.08	0.0798	99.75	95 -105
4	M-F	0.2	0.1953	97.66	95 -105

[redacted]4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Formulation analysis - Day 1 of treatment for Toxicokinetic groups - Content check

STUDY NO.: [redacted]

Group	Sex	Intended Concentration mg/ml	Found Concentration mg/ml	Recovery %	Recovery Limits %
1	M-F	0	0	-	-
4-5	M-F	0.2	0.2079	103.97	95 -105

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Formulation analysis - Week 4 of treatment - Content check

STUDY NO.: [redacted]

Group	Sex	Intended Concentration mg/ml	Found Concentration mg/ml	Recovery %	Recovery Limits %
1	M-F	0	0	-	-
2	M-F	0.03	0.02993	99.76	95 -105
3	M-F	0.08	0.08132	101.65	95 -105
4	M-F	0.2	0.2051	102.57	95 -105

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM IV - Analytical method and validation report for toxicokinetic analysis and toxicokinetic analysis results

STUDY NO. [redacted]

WARNING AND SAFETY PRECAUTIONS

SAFETY

Organic solvents - all organic solvents must be treated as potentially hazardous and all procedures using them must be performed in a fume cupboard.

[redacted]

Appropriate eye protection, impervious gloves and lab coat should be worn.

This method requires the use of corrosive and toxic reagents. It is the responsibility of the analyst to perform the method consistent with safe laboratory practices. The analyst should wear eye protection, impervious gloves, and a lab coat when preparing standards and processing samples. Caution statements have been included in the method giving specific guidance to certain procedural steps. Detailed hazard information should be obtained from the current MSDS available from the manufacturer of the solvent or reagent.

FIRST AID

Solvents, acids and alkalis in contact with skin - wash with copious amounts of cold water. Splashes in the eye - irrigate with water and seek medical attention immediately.
Cuts - seek assistance of first aider immediately.
Burns and frostbite - run affected part under cold water (burns) or tepid water (frostbite) for 10 minutes and seek medical attention.

1. INTRODUCTION

[redacted] is a substance developed by the Sponsor.
[redacted] is a [redacted]

Concentration is calculated considering following % distribution [redacted]

2. SCOPE

The method of analysis describes the detection of [redacted] in rat plasma.

3. **FIELD OF APPLICATION**

The method is described to be used for rat plasma in a range from approximately :
4.87 ng/ml about 4870 ng/ml for [redacted]
0.95 ng/ml about 950 ng/ml for [redacted]
2.35 ng/ml about 2350 ng/ml for [redacted]
0.77 ng/ml about 770 ng/ml for [redacted]
1.16 ng/ml about 1160 ng/ml for [redacted]

4. **REFERENCES**

ISO Standard 78/2-1982 Layout for standards - Part 2: Standard for Chemical Analysis

5. **DEFINITIONS**

[redacted] content is taken to mean the amount [redacted] in rat plasma determined according to the described method and expressed as ng of analyte per ml test sample.

6. **PRINCIPLE**

The method essentially consists of four steps:
- Protein precipitation
- Evaporation
- Dissolution
- LC/MS/MS

7. **REACTIONS**

8. **REAGENTS AND MATERIALS**

Note: The reagents (and equipment) for which examples of their sources are quoted are known to be satisfactory, nevertheless reagents and equipment from other sources may be equally suitable. All the reagents must be of analytical grade or better.

8.1 **Chemicals**

Methanol HPLC grade (Baker 8402)

Water HPLC grade (produced by EASYPURE)

Ammonium Acetate (BDH 271424C)

Acetonitrile (Baker 9017)

Acetic acid (Carlo Erba 401391)

[redacted], can be ordered from the sponsor.

Diclofenac Sodium internal standard

8.2 **Solutions**

8.2.1 Ammonium Acetate 2mM pH=4.75 (100% CH_3COOH):

Weigh 154mg of Ammonium Acetate, add 800mL of water, adjusting to pH = 4.75 (±0.1) with 100% Acetic Acid, transfer to a volumetric flask of 1000mL and adjust to the mark with water.

8.3 **Standard solutions**

8.3.1 [redacted] Stock A:

About 25 mg are transferred into a 25mL volumetric flask and dissolved with methanol obtaining a 1000µg/mL solution

8.3.2 Sol 7A:

1.5mL Stock A are transferred into a 25mL volumetric flask and diluted with methanol obtaining a 60µg/mL solution.

8.3.3 Sol 6A:

2mL Sol 7A are transferred into a 50mL volumetric flask and diluted with methanol obtaining a 2.4µg/mL solution.

8.3.4 Sol 5A:

1.5mL Sol 7A are transferred into a 50mL volumetric flask and diluted with methanol obtaining a 1.8µg/mL solution.

8.3.5 Sol 4A:

3mL Sol 5A are transferred into a 10mL volumetric flask and diluted with methanol obtaining a 0.54µg/mL solution.

8.3.6 Sol 3A:

3mL Sol 4A are transferred into a 10mL volumetric flask and diluted with methanol obtaining a 0.162µg/mL solution.

8.3.7 Sol 2A:

2mL Sol 4A are transferred into a 10mL volumetric flask and diluted with methanol obtaining a 0.108µg/mL solution.

8.3.8 Sol 1A:

1mL Sol 4A is transferred into a 10mL volumetric flask and diluted with methanol obtaining a 0.054µg/mL solution.

8.3.9 Sol XA:

1mL Stock A is transferred into a 20mL volumetric flask and diluted with methanol obtaining a 50µg/mL solution.

8.3.10 Sol YA:

1.7mL Sol 7A are transferred into a 50mL volumetric flask and diluted with methanol obtaining a 2.04µg/mL solution.

8.3.11 Stock ISTD:

About 25 mg of Diclofenac Sodium are transferred into a 25mL volumetric flask and dissolved with methanol obtaining a 1mg/mL solution.

8.3.12 ISTD:

0.5 ml Stock ISTD are transferred into a 100mL volumetric flask and diluted with methanol obtaining a 5µg/mL solution.

8.4 APPARATUS

Analytical balance	Mettler AT 261 Delta range or equivalent
Evaporator	Pierce Reacti-Therm III or equivalent
HPLC	Agilent 1100 or equivalent
Detector(MS/MS)	API 2000 Applied Biosystem
Software	Analyst 1.4 Applied Biosystem
Printer	Hewlett-Packard LaserJet 2200
Column	Phenomenex Gemini 5µm C18 110A 2*150 mm
Centrifuge	ALC 4214 or equivalent
Vortex	New ZX VELP or equivalent
HPLC microvials	
Eppendorff plastic tube 1.5mL	
Volumetric pipettes	
Common glassware	

9. SAMPLING AND SAMPLES

Nature of the Sample; Samples shall be such as to enable the detection of residues in blood.
Size of Sample; The size of the sample must be large enough to allow the method to be carried out and to allow repeat analysis where required.
The samples must be taken and packed in such a way as to allow proper identification in the laboratory.
The method of packing, preservation and transport must maintain the integrity of the sample and not prejudice the results of the examination. Samples for the analysis of [redacted] must be stored at temperatures below -18°C.

10. PROCEDURE

10.1 Blank and unknown samples.

To 100µL of sample 300µL of Acetonitrile are added, vortexed and centrifuged for 5 minutes at 14000 rpm. Organic phase are collected, added 20µL of ISTD and evaporated to dryness under a gentle stream of nitrogen at about 37°C. Samples are reconstituted with 100µL of 70% Eluent A and 30% Eluent B and vortexed for 30 seconds. The liquid phase is transferred into glass HPLC vials and injected.

10.2 Calibration samples

To 100µL of rat plasma an adequate aliquot of working standard solution (see table below) is added.
Samples are then processed as previously described.
Concentrations obtained from the weighed amount of standard are corrected for the following percentage, as request by the Sponsor:

Name	Added	From solution	[redacted] concentration in matrix (ng/mL) [redacted]					ISTD Concentration ng/mL
Std 1	20µL	Sol 1A	≈5	≈2.5	≈1	≈1	≈1	≈1000
Std 2		Sol 2A	≈11	≈5	≈2	≈3	≈2	
Std 3		Sol 3A	≈16	≈8	≈3	≈4	≈2	
Std 4		Sol 4A	≈53	≈25	≈10	≈13	≈8	
Std 5		Sol 5A	≈175	≈85	≈34	≈42	≈28	
Std 6		Sol 6A	≈234	≈113	≈46	≈56	≈37	

10.3 Accuracy and Precision samples (QC samples):

To 100 µL of rat plasma an adequate aliquot of working standard solution (see table below) is added.
Samples are then processed as previously described.
Samples at 10000ng/mL are diluted with blank rat plasma 100-fold obtaining a final concentration of 100ng/mL.
Concentrations obtained from the weighed amount of standard are corrected for the following percentage, as request by the Sponsor:

Name	Added	From solution	[redacted] concentration in matrix (ng/mL) [redacted]					ISTD Concentration (ng/mL)
LLOQ	20µL	Sol 1A	≈5	≈2.5	≈1	≈1	≈1	≈1000
Medium QC		Sol 4A	≈53	≈25	≈10	≈13	≈8	
Low QC		Sol 3A	≈16	≈8	≈3	≈4	≈2	
High QC		Sol YA	≈199	≈96	≈39	≈47	≈31	
Extension level		Sol XA	≈4870	≈2350	≈950	≈1160	≈770	

10.4 **LC-MS/MS and chromatographic conditions:**

10.4.1 Chromatographic Conditions:

	The following HPLC system is set up:
Column:	Phenomenex Gemini 5µm C18 110A 2*150 mm
Column temperature	20°C
Mobile phase:	
Eluent A: (100%	Ammonium acetate 2mM pH=4.75 CH3COOH)
Eluent B:	Acetonitrile
Elution:	Gradient

Time (min.)	Flow (ml/min)	A %	B %
0	0.2	70	30
10	0.2	10	90
15	0.2	10	90
15.10	0.2	70	30
25	0.2	70	30

Flow:	0.2 mL/min
Volume injects:	20µL
Autosampler temperature:	4°C
LC-MS/MS:	
Scan Type:	TurboIon Spray, MRM
Polarity:	Negative

[redacted]	Q1 Mass	Q3 Mass	Retention time minutes
[redacted]	460.9	366.70	≈12.5
	460.9	201.1	
[redacted]	626.80	532.80	≈15.3
	626.80	200.8	
	626.80	366.80	
[redacted]	577.00	482.60	≈14.4
	577.00	200.80	
	577.00	316.50	
[redacted]	792.70	698.60	≈18.0
	792.70	366.70	
	792.70	532.70	
[redacted]	743.00	648.80	≈17.5
	743.00	201.10	
	743.00	482.60	
	743.00	366.60	

Diclofenac Sodium	Q1 Mass	Q3 Mass	Retention time
ISTD	294.10	250.00	≈11.3
	294.10	293.70	

[redacted]

The LC-MS analysis is calibrated using the software Analyst which generates a linear fit calibration curve drawing the best fit of a line to the amounts of [redacted] in ng/mL and the response factor peaks area (Std and ISTD). The software uses linear least-squares fit formula with a 1/X weighting. The result of the fitting is:

$y = A + Bx$

where

A = y-intercept of the calibration curve
B = Slope of the calibration curve
y = Response factor
x = [redacted] amount in ng/mL

Unknown samples are injected after the LC-MS calibration. Results of the [redacted] amount in ng/mL are obtained directly from the LC/MS report. The result is calculated by the software as:

$x = (y-A) / B$

11. EXPRESSION OF RESULTS

[redacted] contents in ng/mL are obtained directly from the chromatogram result table as follows:

$C = x$

Where:

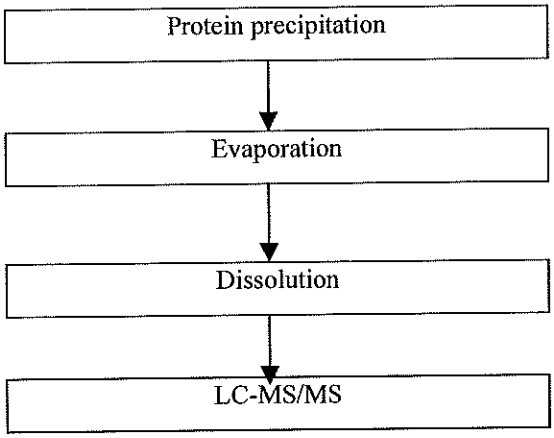
C = content of [redacted] as ng/mL
x = [redacted] amount in ng/mL as read in the chromatogram result table

12. SPECIAL CASES

13. NOTES ON PROCEDURE

14. TEST REPORT

15. **SCHEMATIC REPRESENTATION OF PROCEDURE**



16. **VALIDATION RESULTS** [redacted]

16.1 **Linearity** [redacted] **– MW=**[redacted]

Calibration samples in single at six levels ranging from about 5 ng/mL to 250 ng/mL were processed as described in the analytical method. The following correlation was found:

Added ng/mL	Response (Analyte area/ IS area)	Calculated Concentration (ng/mL)	Deviation %
5.5415	2.84e-002	5.3974	-2.60
11.083	3.48e-002	9.5196	-14.1
16.625	4.76e-002	17.693	6.43
55.415	1.19e-001	63.209	14.1
184.72	2.98e-001	178.21	-3.52
246.29	4.03e-001	245.64	-0.264

Equation: Response = 0.02+0.00156* [redacted]Conc.
r: 0.9981
Response type: area
Fit type: linear
Weighting: 1/X

16.2 **Selectivity** [redacted] **– MW=**[redacted]

For blank plasma samples no interfering peaks were present at the [redacted] retention times.

16.3 **Accuracy and precision**

16.3.1 (Low Level) ([redacted]- MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
16.625	18.019 17.487 17.997 18.642 18.033 17.498	**17.946**	**107.95**	**2.38**
	N =6			

N: number of samples used for calculations.

16.3.2 (Medium Level) ([redacted]- MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
55.415	62.495 60.177 60.995 61.567 61.322 61.370	**61.321**	**110.66**	**1.23**
	N =6			

N: number of samples used for calculations.

16.3.3 (Highest Level) ([redacted]- MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
209.35	219.67 236.85 206.43 217.84 212.56 193.42	**214.46**	**102.44**	**6.76**
	N =6			

N: number of samples used for calculations.

16.3.4 (Extension Level) ([redacted] – MW=[redacted]

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
5131.0	4397.6 4708.7 5199.3 5137.5 4669.2 5483.7	**4932.7**	**96.13**	**8.22**
	N =6			

N: number of samples used for calculations.

16.4 Lower Limit of Quantification (LLOQ) [redacted]

The lowest standard on the calibration curve (5.5415 ng/mL) fulfilling the requirements for accuracy and precision will be considered as the Lower Limit of Quantification.

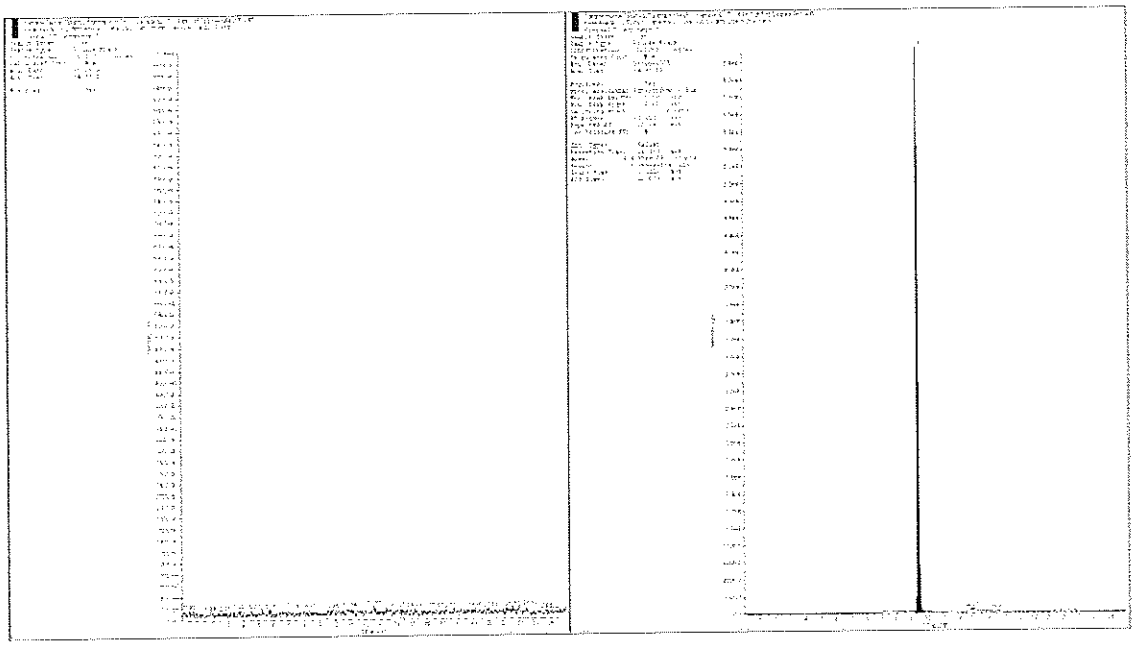
16.4.1 LLOQ ([redacted] – MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

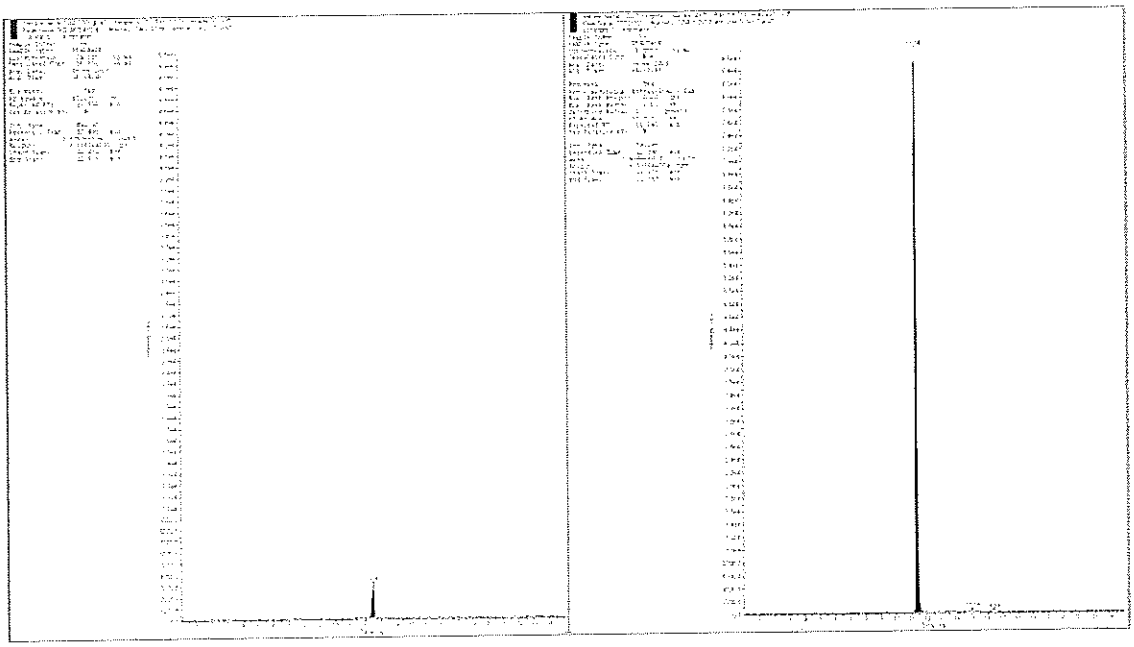
Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
5.5415	4.7846 5.7921 5.4189 4.8233 4.5419 4.7123	**5.0122**	**90.45**	**9.66**
	N =6			

N: number of samples used for calculations.

16.5 Chromatogram of a blank plasma rat ([redacted]– MW=[redacted])



16.6 Chromatogram of a spiked plasma rat at approximately 16 ng/mL ([redacted]- MW=[redacted])



17. **VALIDATION RESUTS (N3)**

17.1 **Linearity ([redacted]- MW=[redacted])**

Calibration samples in single at six levels ranging from about 2 ng/mL to 120 ng/mL were processed as described in the analytical method. The following correlation was found:

Added ng/mL	Response (Analyte area/ IS area)	Calculated Concentration (ng/mL)	Deviation %
2.6740	2.06E-02	2.5582	-4.33
5.3481	3.52E-02	5.6827	6.26
8.0221	4.33E-02	7.4030	-7.72
26.740	1.43E-01	28.716	7.39
89.135	4.21E-01	88.171	-1.08
118.85	5.62E-01	118.23	-0.515

Equation Response: 0.00866+0.00468* [redacted]Conc.
r: 0.9994
Response type: area
Fit type: linear
Weighting: 1/X

17.2 **Selectivity ([redacted]- MW=[redacted])**

For blank plasma samples no interfering peaks were present at the [redacted]retention times.

17.3 **Accuracy and precision**

17.3.1 (Low Level) ([redacted]- MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
8.0221	8.4086 8.5280 8.6370 8.9212 8.3437 8.4171	**8.5426**	**106.49**	**2.49**
	N =6			

N: number of samples used for calculations.

17.3.2 (Medium Level) [redacted] – MW=[redacted]

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
26.740	25.840 27.778 24.641 23.775 27.243 23.791	**25.511**	**95.40**	**6.78**
	N =6			

N: number of samples used for calculations.

17.3.3 (Highest Level) ([redacted]– MW=[redacted]

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
101.02	99.759 113.24 90.040 97.151 101.86 91.187	**98.873**	**97.88**	**8.54**
	N =6			

N: number of samples used for calculations.

17.3.4 (Extension Level) ([redacted] – MW=[redacted]

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
2476.0	2119.1 2110.7 2214.3 2315.9 2231.4 2118.3	**2184.95**	**88.25**	**3.80**
	N =6			

N: number of samples used for calculations.

17.4 **Lower Limit of Quantification (LLOQ) ([redacted]- MW=[redacted])**

The lowest standard on the calibration curve (2.6740 ng/mL) fulfilling the requirements for accuracy and precision will be considered the Lower Limit of Quantification.

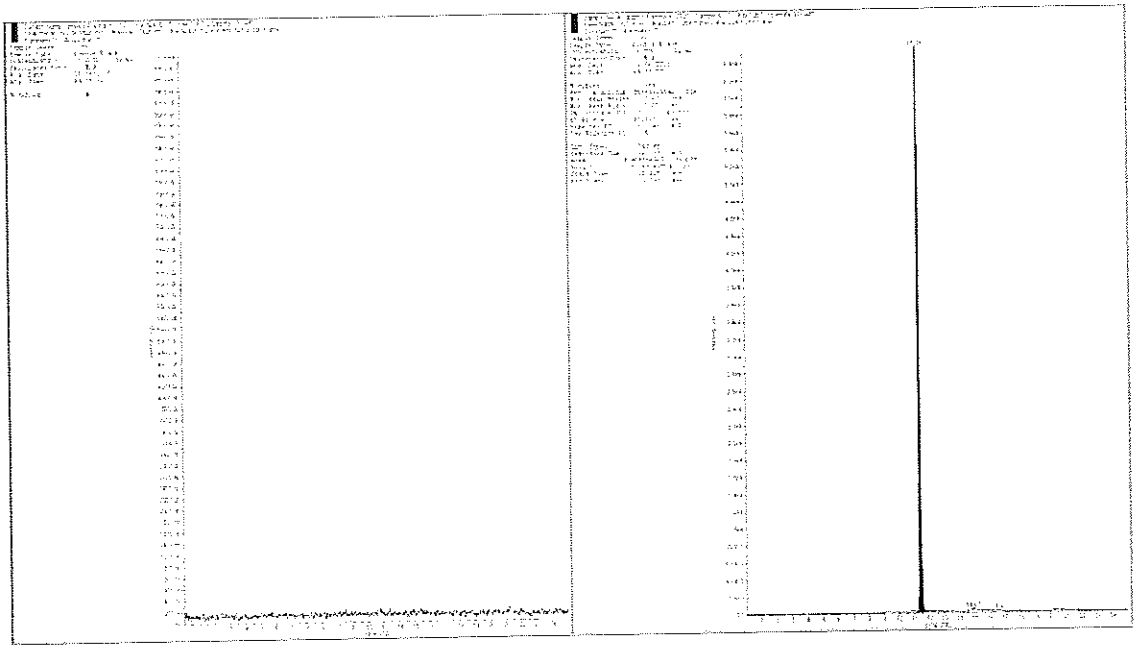
17.4.1 LLOQ ([redacted]- MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

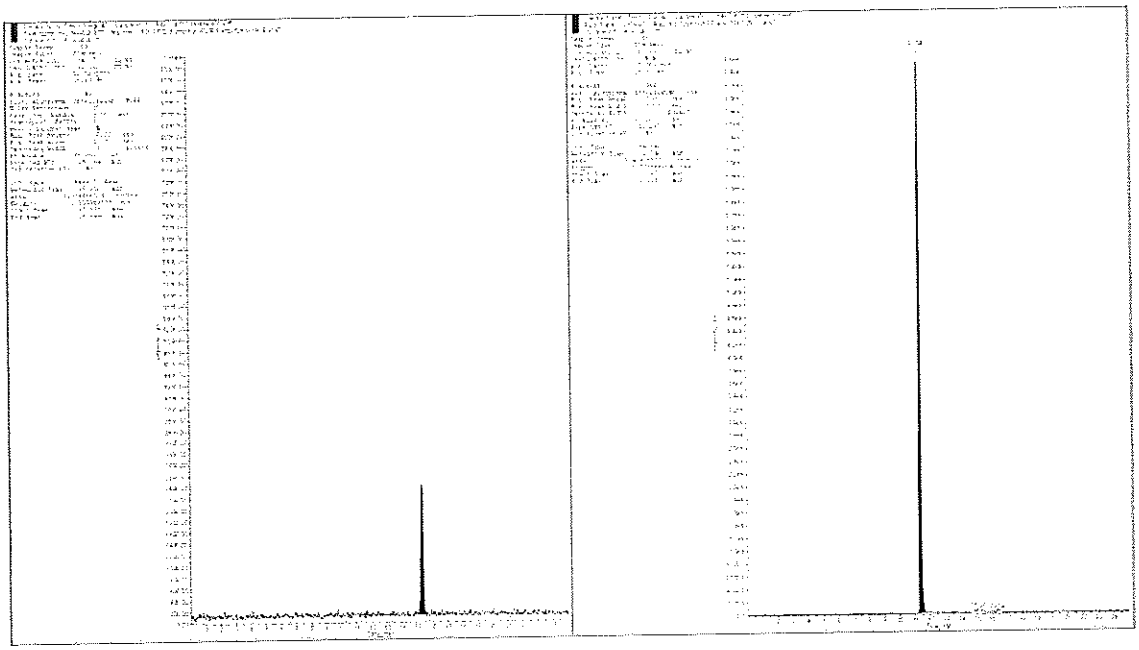
Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
2.6740	2.3270 2.6339 2.6694 2.6038 2.4944 2.8923	**2.6035**	**97.36**	**7.23**
	N =6			

N: number of samples used for calculations.

17.5 Chromatogram of a blank plasma rat ([redacted]- MW=[redacted])



17.6 Chromatogram of a spiked plasma rat at approximately 8 ng/mL ([redacted]- MW=[redacted])



18. **VALIDATION RESULTS** [redacted]

18.1 **Linearity** [redacted] **– MW=**[redacted]

Single calibration samples at six levels ranging from about 1 ng/mL to 50 ng/mL were processed as described in the analytical method. The following correlation was found:

Added ng/mL	Response (Analyte area/ IS area)	Calculated Concentration (ng/mL)	Deviation %
1.0810	3.00E-03	1.1074	2.44
2.1620	4.40E-03	2.1877	1.19
3.2430	5.82E-03	3.2888	1.41
10.810	1.48E-02	10.246	-5.22
36.033	4.67E-02	34.882	-3.20
48.044	6.59E-02	49.662	3.37

Equation: Response = 0.00156+0.00129* [redacted] Conc.
r: 0.9993
Response type: area
Fit type: linear
Weighting: 1/X

18.2 **Selectivity (**[redacted]**– MW=**[redacted]**)**

For blank plasma samples no interfering peaks were present at the [redacted] retention times.

18.3 **Accuracy and precision**

18.3.1 (Low Level) ([redacted]– MW=[redacted]

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
3.2430	3.3630 3.3856 3.4315 3.2653 3.2342 3.0899	**3.2949**	**101.60**	**3.79**
	N =6			

N: number of samples used for calculations.

18.3.2 (Medium Level) ([redacted] – MW=[redacted]0)

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
10.810	12.209 12.114 11.411 11.807 11.617 10.875	**11.672**	**107.97**	**4.21**
	N =6			

N: number of samples used for calculations.

18.3.3 (Highest Level) ([redacted] – MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
40.838	38.312 41.983 34.966 35.516 36.067 34.825	**36.945**	**90.47**	**7.51**
	N =6			

N: number of samples used for calculations.

18.3.4 (Extension Level) ([redacted] – MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
1000.9	1004.1 1039.6 859.19 1006.2 931.27 1003.9	**974.04**	**97.32**	**6.83**
	N =6			

N: number of samples used for calculations.

18.4 **Lower Limit of Quantification (LLOQ) ([redacted]– MW=[redacted])**

The lowest standard on the calibration curve (1.0810 ng/mL) fulfilling the requirements for accuracy and precision will be considered as the Lower Limit of Quantification.

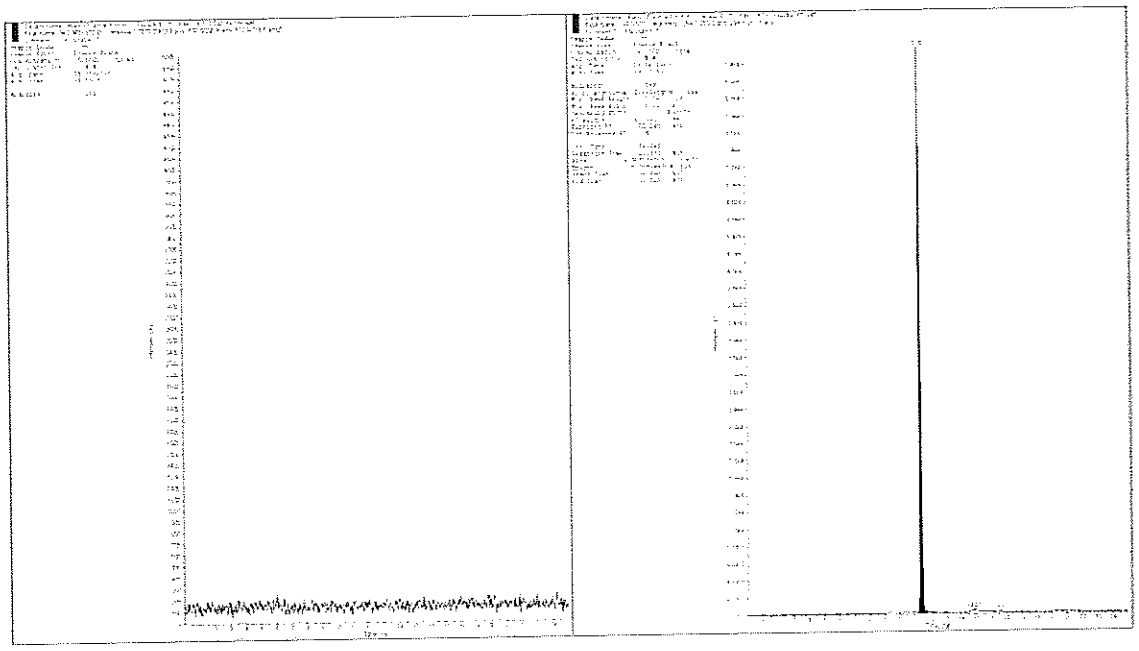
18.4.1 LLOQ ([redacted]– MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

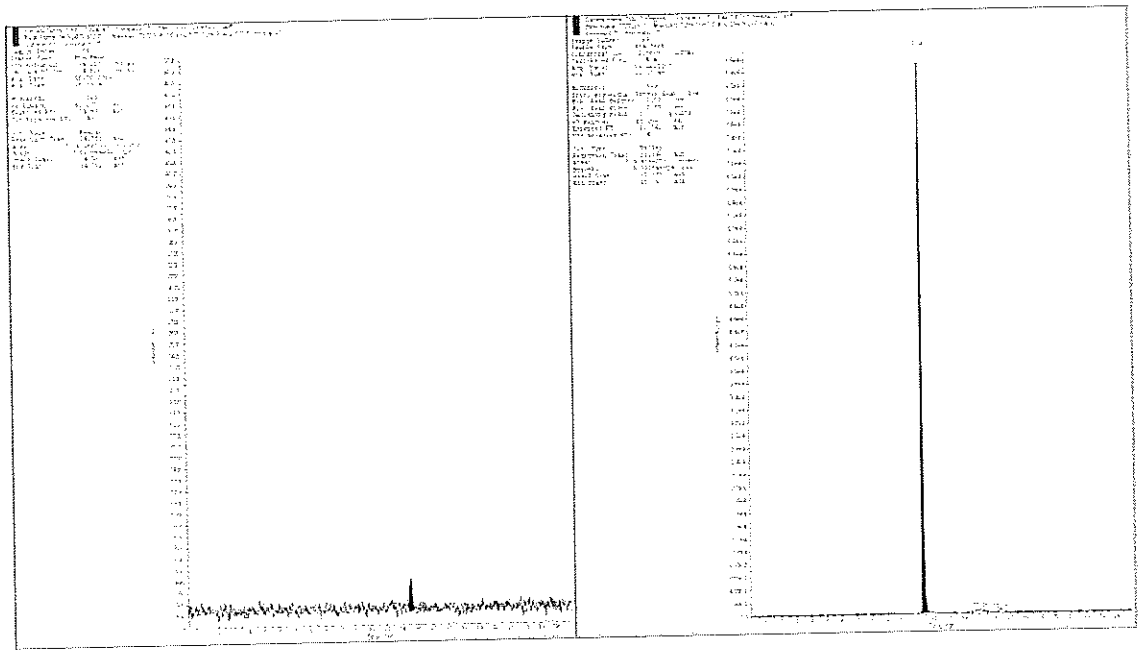
Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
1.0810	0.9127 1.0280 0.93807 0.94814 1.2206 0.94077	**0.99805**	**92.33**	**11.61**
	N =6			

N: number of samples used for calculations.

18.5 Chromatogram of a blank plasma rat [redacted] – MW=[redacted]



18.6 Chromatogram of a spiked plasma rat at approximately 3 ng/mL ([redacted] – MW[redacted]



19. **VALIDATION RESULTS ([redacted])**

19.1 **Linearity ([redacted] – MW=[redacted])**

Calibration samples in single at six levels ranging from about 1 ng/mL to 60 ng/mL were processed as described in the analytical method. The following correlation was found:

Added ng/mL	Response (Analyte area/ IS area)	Calculated Concentration (ng/mL)	Deviation %
1.3200	5.44E-03	1.2038	-8.80
2.6399	9.90E-03	2.9416	11.4
3.9599	1.29E-02	4.1094	3.78
13.200	3.36E-02	12.176	-7.75
43.998	1.16E-01	44.303	0.693
58.664	1.54E-01	59.048	0.653

Equation: Response = 0.00234+0.00257* [redacted] Conc.
r: 0.9993
Response type: area
Fit type: linear
Weighting: 1/X

19.2 **Selectivity ([redacted] – MW=[redacted])**

For blank plasma samples no interfering peaks were present at the [redacted] retention times.

19.3 **Accuracy and precision**

19.3.1 (Low Level) [redacted] – MW=[redacted]

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
3.9599	4.2629 4.2755 4.3215 4.2502 4.0866 4.4008	**4.2663**	**107.74**	**2.43**
	N =6			

N: number of samples used for calculations.

19.3.2 (Medium Level) ([redacted] – MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
13.200	12.336 13.296 11.630 11.982 13.093 13.195	**12.589**	**95.37**	**5.59**
	N =6			

N: number of samples used for calculations.

19.3.3 (Highest Level) ([redacted] – MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
49.865	44.614 52.486 43.682 45.674 46.587 43.497	**46.090**	**92.43**	**7.26**
	N =6			

N: number of samples used for calculations.

19.3.4 (Extension Level) ([redacted] – MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
1222.2	1376.3 1377.4 1080.2 1109.7 1117.9 1163.5	**1204.2**	**98.52**	**11.33**
	N =6			

N: number of samples used for calculations.

19.4 **Lower Limit of Quantification (LLOQ) [redacted] – MW=[redacted]**

The lowest standard on the calibration curve (1.3200 ng/mL) fulfilling the requirements for accuracy and precision will be considered as the Lower Limit of Quantification.

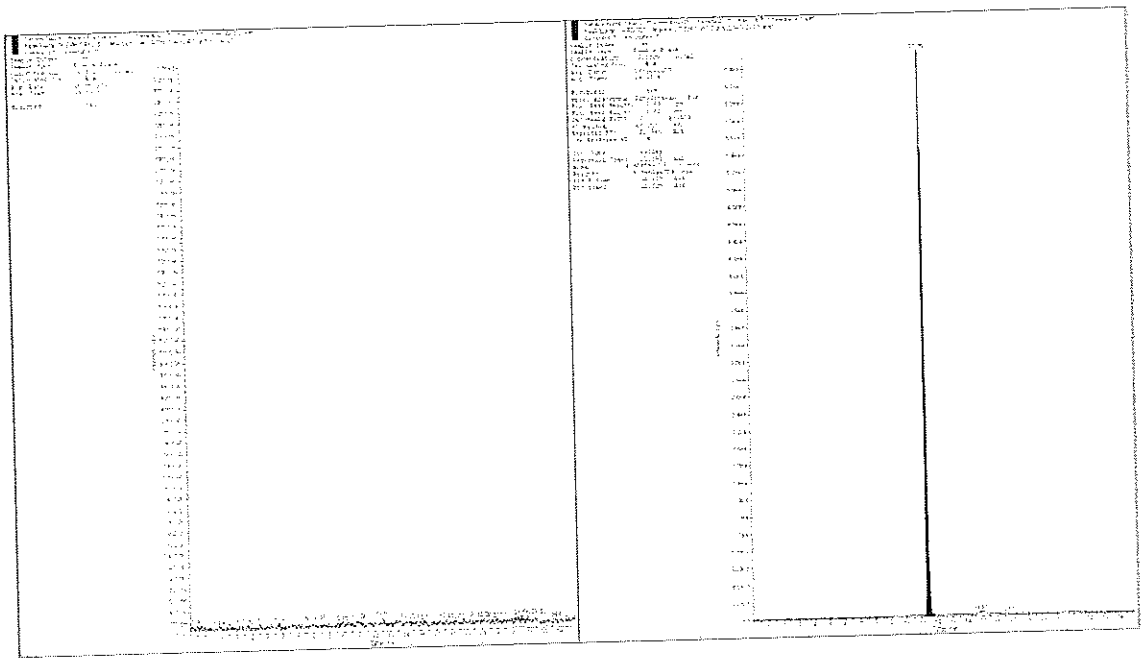
19.4.1 LLOQ [redacted] – MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

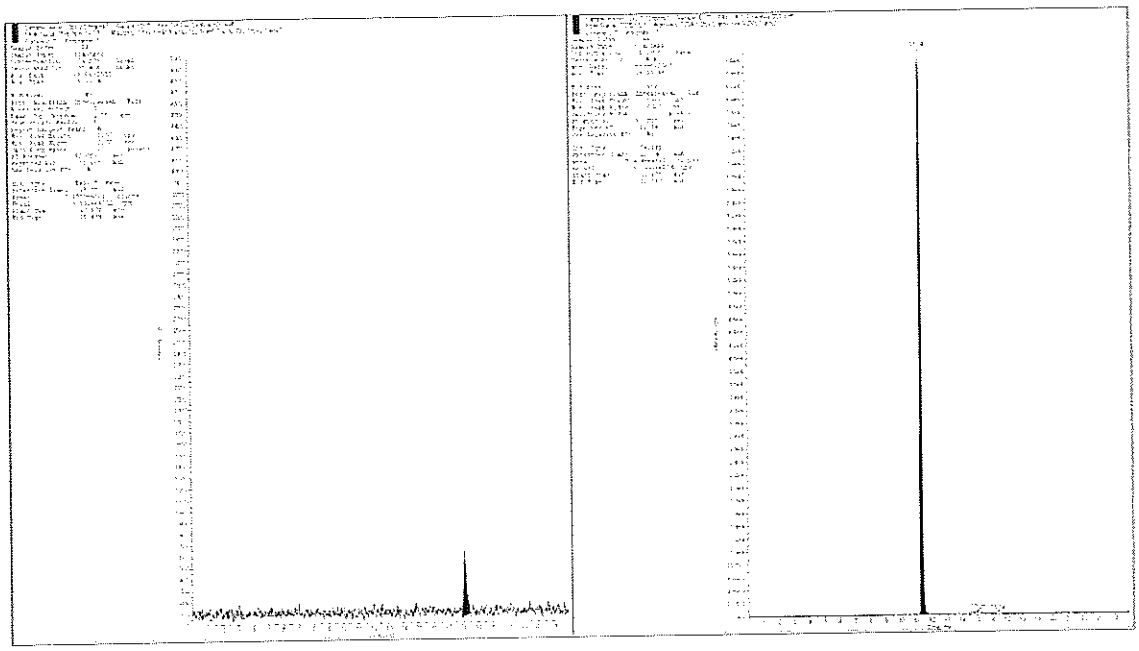
Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
1.3200	1.2470 1.2584 1.1957 1.3730 1.3715 1.4375	**1.3139**	**99.54**	**7.11**
	N =6			

N: number of samples used for calculations.

19.5 Chromatogram of a blank plasma rat ([redacted]– MW=[redacted])



19.6 Chromatogram of a spiked plasma rat at approximately 4 ng/mL [redacted]– MW=[redacted]



20. **VALIDATION RESULTS ([redacted])**

20.1 **Linearity ([redacted] – MW=[redacted])**

Calibration samples in single at six levels ranging from about 1 ng/mL to 40 ng/mL were processed as described in the analytical method. The following correlation was found:

Added ng/mL	Response (Analyte area/ IS area)	Calculated Concentration (ng/mL)	Deviation %
0.87617	6.32E-03	0.78661	-10.2
1.7523	1.02E-02	1.8726	6.86
2.6285	1.33E-02	2.7491	4.59
8.7617	3.43E-02	8.6386	-1.41
29.206	1.09E-01	29.498	1.00
38.941	1.41E-01	38.621	-0.823

Equation: Response = 0.00352+0.00356* [redacted] Conc.
r: 0.9998
Response type: area
Fit type: linear
Weighting: 1/X

20.2 **Selectivity ([redacted] – MW=[redacted])**

For blank plasma samples no interfering peaks were present at the [redacted]etention times.

20.3 **Accuracy and precision**

20.3.1 (Low Level) ([redacted] – MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
2.6285	2.8893 2.4930 2.2794 2.8361 2.6955 2.4138	**2.6012**	**98.96**	**9.38**
	N =6			

N: number of samples used for calculations.

20.3.2 (Medium Level) [redacted] – MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
8.7617	9.7568 9.4218 9.7209 10.066 9.5491 9.6688	**9.6972**	**110.68**	**2.25**
	N =6			

N: number of samples used for calculations.

20.3.3 (Highest Level) ([redacted] – MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
33.100	31.142 33.540 30.338 30.767 31.298 28.709	**30.966**	**93.55**	**5.06**
	N =6			

N: number of samples used for calculations.

20.3.4 (Extension Level) [redacted] – MW=[redacted]

Sextuplicates at the following concentrations were prepared and analysed:

Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
811.27	740.62 709.40 733.32 902.32 865.16 773.23	**787.34**	**97.05**	**9.94**
	N =6			

N: number of samples used for calculations.

20.4 **Lower Limit of Quantification (LLOQ) [redacted]– MW=[redacted])**

The lowest standard on the calibration curve (0.87617 ng/mL) fulfilling the requirements for accuracy and precision will be considered as the Lower Limit of Quantification.

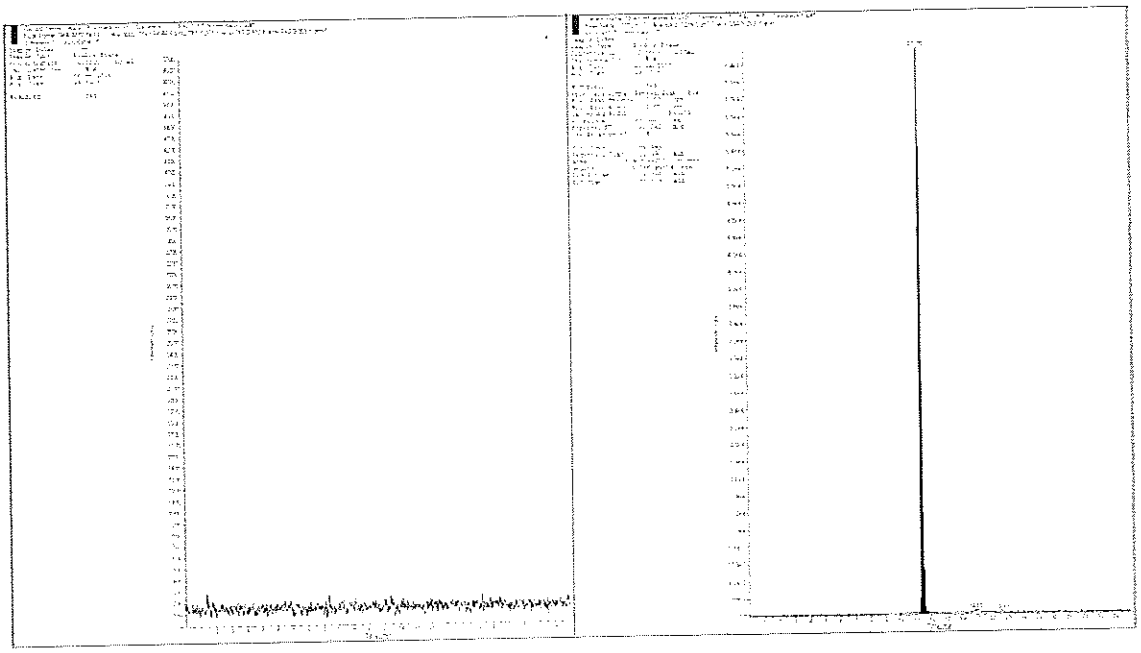
20.4.1 LLOQ ([redacted]– MW=[redacted])

Sextuplicates at the following concentrations were prepared and analysed:

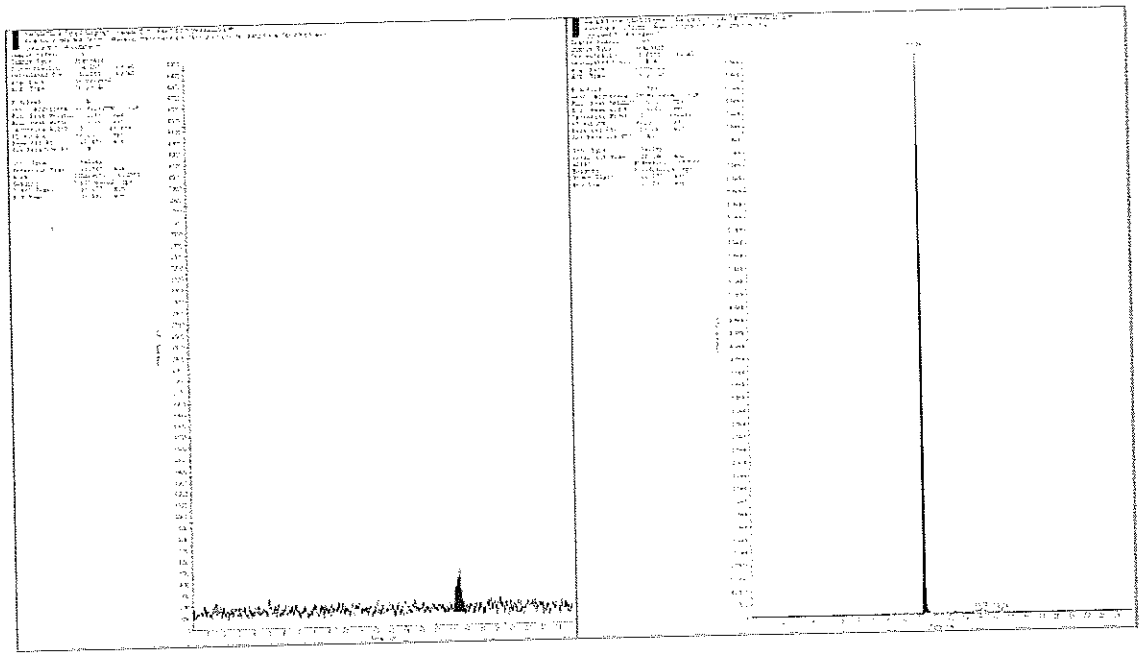
Amount added	Amount found		Accuracy	Precision
ng/mL	ng/mL	Mean (ng/mL)	%	CV %
0.87617	0.85838 0.87324 0.82732 0.77801 0.80079 0.89631	**0.83903**	**95.76**	**5.37**
	N =6			

N: number of samples used for calculations.

20.5 Chromatogram of a blank plasma rat [redacted] – MW=[redacted]



20.6 Chromatogram of a spiked plasma rat at approximately 2.6 ng/mL ([redacted]– MW=[redacted])



[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - Plasma levels of [redacted] (ng/ml) following oral administration of [redacted] (2.0 mg/kg) to male rats

STUDY NO.: [redacted]

Animal No.	Sampling times (hours post-dose)								
	0	2	4	6	8	24	48	168	216
367100062	BLOQ		272.82 D			270.06 D			
367100064	BLOQ		51.762 D+			417.51 D			
367100066	BLOQ		197.66 D			423.02 D			
367100068		198.45 D			347.29 D			226.83 D	
367100070		155.69 D			333.65 D			298.65 D	
367100072		227.64 D			318.77 D			275.77 D	
367100074				334.38 D			352.73 D		274.02 D
367100076				358.60 D			274.21 D		283.70 D
367100078				305.38 D			374.31 D		336.99 D
MEAN	0	193.93	235.24	332.79	333.24	370.20	333.75	267.08	298.24
SD	0	36.188	37.58	26.646	14.264	86.765	52.68	36.69	33.909
CV %	0	18.66	15.98	8.01	4.28	23.44	15.78	13.74	11.37

+ = Values giving a CV > 50% were not included in the calculation of mean, standard deviation and CV (coefficient of variation)
BLOQ = below the limit of quantitation
D = diluted sample

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - Plasma levels of [redacted] (ng/ml) following oral administration of [redacted] (2.0 mg/kg) to female rats

STUDY NO.: [redacted]

Animal No.	Sampling times (hours post-dose)								
	0	2	4	6	8	24	48	168	216
36710061	BLOQ		219.27 D			443.95 D			
36710063	BLOQ		262.80 D			406.66 D			
36710065	BLOQ		245.32 D			291.57 D			
36710067		226.84 D			351.20 D			724.52 D@	
36710069		219.66 D			272.03 D			290.72 D	
36710071		460.15 D			312.69 D			402.21 D	
36710073				299.87 D			27.695 D +@		327.04 D
36710075				286.84 D			273.33 D		222.99 D
36710077				264.54 D			276.44 D		211.62 D
Mean	0	302.22	242.46	283.75	311.97	380.73	274.89	472.48	253.88
SD	0	136.82	21.905	17.867	39.59	79.431	N/C	225.28	63.61
CV%	0	45.27	9.03	6.30	12.69	20.86	N/C	47.68	25.06

+ = Values giving a CV > 50% were not included in the calculation of mean, standard deviation and CV (coefficient of variation)
BLOQ = below the limit of quantitation N/C = Not calculable due to low number of samples
D = diluted sample
@ = Estimated samples since concentration was out of validation range

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - Plasma levels of [redacted] (ng/ml) following oral administration of [redacted] (2.0 mg/kg) to male rats

STUDY NO.: [redacted]

Animal No.	Sampling times (hours post-dose)								
	0	2	4	6	8	24	48	168	216
367100062	BLOQ		128.45 D			80.697 D			
367100064	BLOQ		23.363 D +			135.25 D			
367100066	BLOQ		71.903 D			156.93 D			
367100068		87.360 D			125.80 D			69.159 D	
367100070		71.018 D			124.01 D			99.273 D	
367100072		111.58 D			117.50 D			105.46 D	
367100074				113.81 D			114.51 D		85.463 D
367100076				142.92 D			91.774 D		85.350 D
367100078				114.89 D			146.98 D		98.285 D
MEAN	0	89.986	100.18	123.87	122.44	124.29	117.75	91.297	89.699
SD	0	20.408	N/C	16.504	4.368	39.28	27.746	19.42	7.4356
CV %	0	22.68	N/C	13.32	3.57	31.60	23.56	21.27	8.29

+ = Values giving a CV > 50% were not included in the calculation of mean, standard deviation and CV (coefficient of variation)
BLOQ = below the limit of quantitation
D = diluted sample
N/C = Not calculable due to low number of samples

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - Plasma levels of [redacted] (ng/ml) following oral administration of [redacted] (2.0 mg/kg) to female rats

STUDY NO.: [redacted]

Animal No.	Sampling times (hours post-dose)								
	0	2	4	6	8	24	48	168	216
367100061	BLOQ		94.877 D			168.59 D			
367100063	BLOQ		94.685 D			173.82 D			
367100065	BLOQ		113.98 D			139.76 D			
367100067		91.680 D			115.97 D			222.77 D	
367100069		111.55 D			122.81 D			102.47 D	
367100071		169.50 D			134.02 D			122.41 D	
367100073				106.50 D			10.901 D +		83.530 D
367100075				119.92 D			114.74 D		71.525 D
367100077				109.39 D			86.232 D		68.156 D
MEAN	0	124.24	101.18	111.94	124.27	160.72	100.49	149.22	74.404
SD	0	40.433	11.085	7.0632	9.1127	18.342	N/C	64.475	8.0812
CV %	0	32.54	10.96	6.31	7.33	11.41	N/C	43.21	10.86

+ = Values giving a CV > 50% were not included in the calculation of mean, standard deviation and CV (coefficient of variation)
BLOQ = below the limit of quantitation N/C = Not calculable due to low number of samples
D = diluted sample
@ = Estimated samples since concentration was out of validation range

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - Plasma levels of [redacted] (ng/ml) following oral administration of [redacted] (2.0 mg/kg) to male rats

STUDY NO.: [redacted]

Animal No.	Sampling times (hours post-dose)								
	0	2	4	6	8	24	48	168	216
367100062	BLOQ		3993.2 D@			3665.2 D@			
367100064	BLOQ		610.10 D +			5087.8 D@			
367100066	BLOQ		2885.3 D@			4883.2 D@			
367100068		3740.1 D@			3908.0 D@			2350.1 D@	
367100070		2639.1 D@			4008.6 D@			3414.4 D@	
367100072		3983.7 D@			3726.3 D@			3779.5 D@	
367100074				4246.0 D@			4108.3 D@		3436.4 D@
367100076				4519.3 D@			3585.9 D@		3576.0 D@
367100078				3979.1 D@			4457.8 D@		3610.5 D@
MEAN	0	3454.3	3439.25	4248.1	3881.0	4545.4	4050.7	3181.3	3541.0
SD	0	716.41	N/C	270.11	143.08	769.11	438.8	742.65	92.186
CV %	0	20.74	N/C	6.36	3.69	16.92	10.83	23.34	2.60

+ = Values giving a CV > 50% were not included in the calculation of mean, standard deviation and CV (coefficient of variation)
BLOQ = below the limit of quantitation N/C = Not calculable due to low number of samples
D = diluted sample
@ = Estimated samples since concentration was out of validation range

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - Plasma levels of [redacted] (ng/ml) following oral administration of [redacted] (2.0 mg/kg) to female rats

STUDY NO.: [redacted]

Animal No.	Sampling times (hours post-dose)								
	0	2	4	6	8	24	48	168	216
367100061	BLOQ		3355.3 D@			2634.5 D			
367100063	BLOQ		4056.8 D@			2540.1 D			
367100065	BLOQ		3431.4 D@			1753.8 D			
367100067		3872.9 D@			4082.3 D@			1841.4 D +	
367100069		3892.7 D@			3541.0 D@			112.37 D	
367100071		5978.3 D@			3433.9 D@			65.342 D@	
367100073				3591.0 D@			129.97 D +		180.72 D@
367100075				3365.2 D@			697.68 D		143.68 D@
367100077				3801.1 D@			804.80 D		109.57 D@
MEAN	0	4581.3	3614.5	3585.8	3685.7	2309.5	751.24	88.86	144.66
SD	0	1209.9	384.93	218	347.59	483.53	N/C	N/C	35.585
CV %	0	26.41	10.65	6.08	9.43	20.94	N/C	N/C	24.60

+ = Values giving a CV > 50% were not included in the calculation of mean, standard deviation and CV (coefficient of variation)
BLOQ = below the limit of quantitation N/C = Not calculable due to low number of samples
D = diluted sample
@ = Estimated samples since concentration was out of validation range

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - Plasma levels of [redacted] (ng/ml) following oral administration of [redacted] (2.0 mg/kg) to male rats

STUDY NO.: [redacted]

Animal No.	Sampling times (hours post-dose)								
	0	2	4	6	8	24	48	168	216
367100062	BLOQ		610.91 D			490.64 D			
367100064	BLOQ		52.358 D +			803.64 D			
367100066	BLOQ		365.26 D			773.47 D			
367100068		401.62 D			575.61 D			421.93 D	
367100070		330.30 D			580.95 D			588.03 D	
367100072		483.01 D			526.60 D			537.81 D	
367100074				592.06 D			672.71 D		502.11 D
367100076				662.64 D			529.57 D		527.52 D
367100078				547.87 D			717.57 D		532.05 D
MEAN	0	404.98	488.09	600.86	561.05	689.25	639.95	515.92	520.56
SD	0	76.410	N/C	57.888	29.957	172.66	98.188	85.186	16.138
CV %	0	18.87	N/C	9.63	5.34	25.05	15.34	16.51	3.10

+ = Values giving a CV > 50% were not included in the calculation of mean, standard deviation and CV (coefficient of variation)
BLOQ = below the limit of quantitation
D = diluted sample
N/C = Not calculable due to low number of samples

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - Plasma levels of [redacted] (ng/ml) following oral administration of [redacted] (2.0 mg/kg) to female rats

STUDY NO.: [redacted]

Animal No.	Sampling times (hours post-dose)								
	0	2	4	6	8	24	48	168	216
367100061	BLOQ		428.06 D			785.91 D			
367100063	BLOQ		504.46 D			757.38 D			
367100065	BLOQ		487.53 D			582.84 D			
367100067		479.71 D			572.51 D			1199.9 D	
367100069		491.71 D			478.95 D			462.11 D	
367100071		831.97 D			528.48 D			659.40 D	
367100073				496.46 D			26.422 D + @		509.47 D
367100075				527.13 D			497.41 D		385.93 D
367100077				458.37 D			442.23 D		341.14 D
MEAN	0	601.13	473.35	493.99	526.65	708.71	469.82	773.8	412.18
SD	0	200.00	40.125	34.447	46.807	109.94	N/C	381.97	87.181
CV %	0	33.27	8.48	6.97	8.89	15.51	N/C	49.36	21.15

+ = Values giving a CV > 50% were not included in the calculation of mean, standard deviation and CV (coefficient of variation)
BLOQ = below the limit of quantitation N/C = Not calculable due to low number of samples
D = diluted sample
@ = Estimated samples since concentration was out of validation range

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - Plasma levels of [redacted] (ng/ml) following oral administration of [redacted] (2.0 mg/kg) to male rats

STUDY NO.: [redacted]

Animal No.	Sampling times (hours post-dose)								
	0	2	4	6	8	24	48	168	216
367100062	BLOQ		225.72 D			123.49 D			
367100064	BLOQ		19.703 D +			202.99 D			
367100066	BLOQ		132.50 D			238.7 D			
367100068		109.93 D			174.67 D			86.516 D	
367100070		91.728 D			181.71 D			114.77 D	
367100072		176.81 D			190.45 D			133.95 D	
367100074				192.85 D			176.32 D		82.499 D
367100076				224.66 D			132.5 D		84.915 D
367100078				173.11 D			221.07 D		113.91 D
MEAN	0	126.16	179.11	196.87	182.28	188.39	176.63	111.75	93.775
SD	0	44.802	N/C	26.009	7.9052	58.976	44.286	23.861	17.48
CV %	0	35.51	N/C	13.21	4.34	31.31	25.07	21.35	18.64

+ = Values giving a CV > 50% were not included in the calculation of mean, standard deviation and CV (coefficient of variation)
BLOQ = below the limit of quantitation
D = diluted sample
N/C = Not calculable due to low number of samples

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - Plasma levels of [redacted] (ng/ml) following oral administration of [redacted] (2.0 mg/kg) to female rats

STUDY NO.: [redacted]

Animal No.	Sampling times (hours post-dose)								
	0	2	4	6	8	24	48	168	216
367100061	BLOQ	149.91 D	171.30 D	168.77 D	194.63 D	250.66 D	13.844 D +	266.49 D +	78.458 D
367100063	BLOQ	153.27 D	169.55 D	188.72 D	182.27 D	266.05 D	129.08 D	101.56 D	85.968 D
367100065	BLOQ	269.28 D	209.91 D	148.40 D	198.66 D	187.36 D	108.22 D	118.98 D	61.082 D
367100067									
367100069									
367100071									
367100073									
367100075									
367100077									
MEAN	0	190.82	183.59	168.63	191.85	234.69	118.65	110.27	75.169
SD	0	67.969	22.813	20.16	8.5405	41.705	N/C	N/C	12.765
CV %	0	35.62	12.43	11.96	4.45	17.77	N/C	N/C	16.98

+ = Values giving a CV > 50% were not included in the calculation of mean, standard deviation and CV (coefficient of variation)
BLOQ = below the limit of quantitation
D = diluted sample
N/C = Not calculable due to low number of samples

[redacted]-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - Toxicokinetic parameters

STUDY NO.: [redacted]

Males

Dose level (mg/kg)	[redacted]				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(24-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
2.0	24	370.2	544	65550	299662
	[redacted]				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(24-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	24	124.3	385	22516	72388
	[redacted]				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(24-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	24	4545.4	481	791984	3249932
	[redacted]				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(24-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	24	689.3	454	123729	464508
	[redacted]				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(6-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	6	196.9	201	30768	57915

* Calculated from t_{max}

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Toxicokinetic analysis - Toxicokinetic parameters

STUDY NO.: [redacted]

Females

Dose level (mg/kg)	[redacted]				
	t_{max} (h)	C_{max} (ng/ml)	°T ½ (h)	°$AUC_{(24-216)}$ (ng/ml·h)	°$AUC_{(inf)}$ (ng/ml·h)
2.0	168	472.5	2185	77653	877949
	[redacted]				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(24-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	24	160.7	346	26563	63751
	[redacted]				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(2-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	2	4581.3	39	167950	176042
	[redacted]				
	t_{max} (h)	C_{max} (ng/ml)	°T ½ (h)	°$AUC_{(24-216)}$ (ng/ml·h)	°$AUC_{(inf)}$ (ng/ml·h)
	168	773.8	763	130770	584697
	[redacted]				
	t_{max} (h)	C_{max} (ng/ml)	*T ½ (h)	*$AUC_{(24-216)}$ (ng/ml·h)	*$AUC_{(inf)}$ (ng/ml·h)
	24	234.7	160	27116	44431

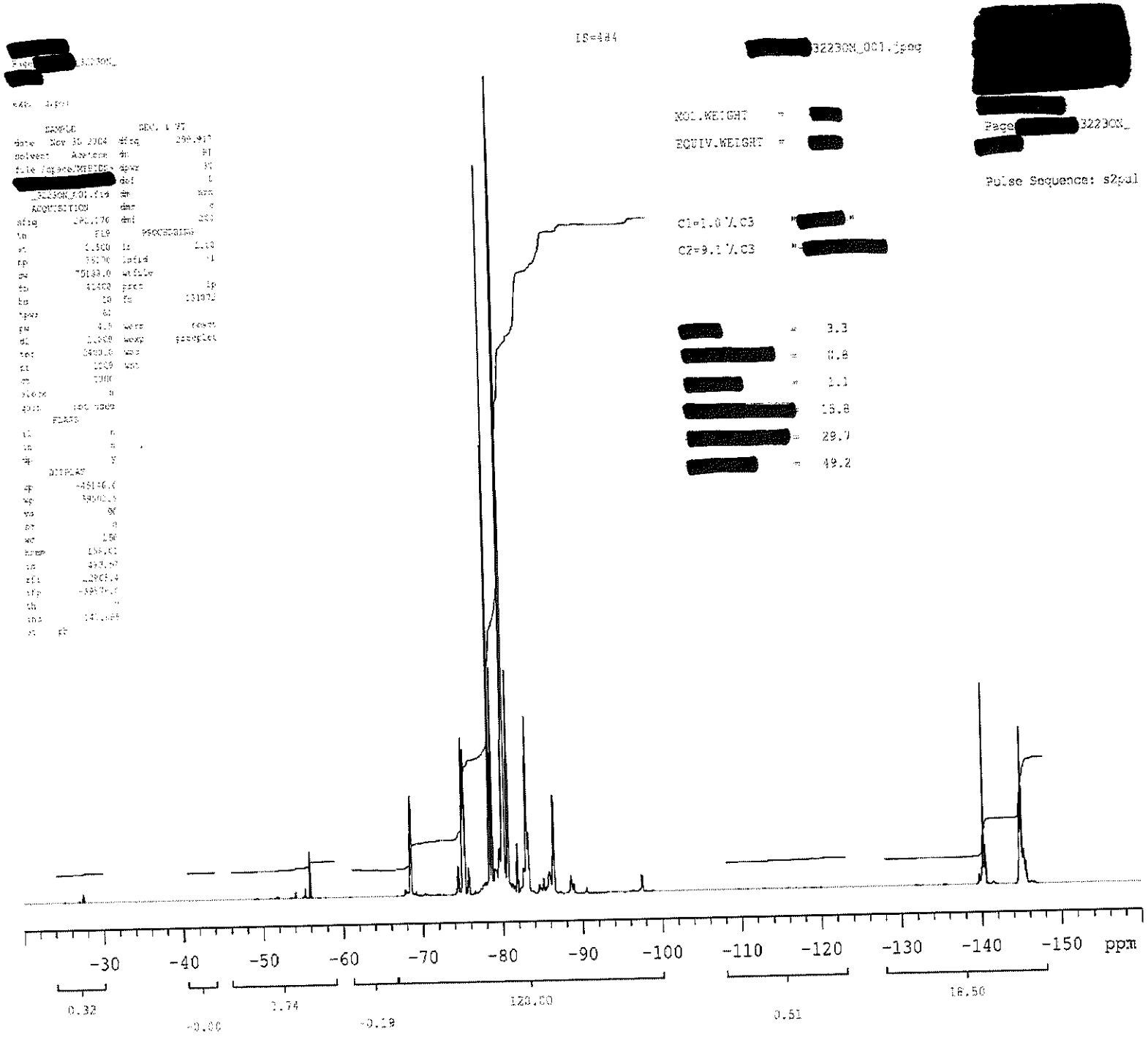
* Calculated from t_{max}
° Calculated from 24 hours

[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM V - Certificate of analysis

STUDY NO.: [redacted]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EQUIV.WEIGHT =
Pulse Sequence: s2pul
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
ppm
0.32
1.74
120.00
0.51
16.50

[redacted]: 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM VI - Study protocol

STUDY NO.: [redacted]

[redacted]

[redacted]

4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

Final Protocol
prepared for

[redacted]

by

[redacted]

March 2005

[redacted]

[redacted]

[redacted]

[redacted]

1. INTRODUCTION

1.1 Objective

The purpose of this study is to evaluate the toxicity of [redacted] in rats after daily oral administration for 4 weeks and recovery from any treatment related effects during a recovery period of 2 weeks.

1.2 Species

The Sprague Dawley rat is the species and strain of choice because it is accepted by many regulatory authorities and there is ample experience and background data on this species and strain.

1.3 Route of administration

The test item will be administered by oral route. The oral route has been selected as it is a possible route of exposure of the test item in man.

1.4 Regulatory compliance

This study will be conducted in compliance with the GLP regulations of:

- Commission Directive 1999/11/EC of 8 March 1999 (adoption of the "OECD principles on Good Laboratory Practice - as revised in 1997") and subsequent revisions.
- Decreto Legislativo no. 120 of 27 January 1992 and subsequent revisions.

This study design is in agreement with the procedures described in OECD Guideline no. 407 adopted 27 July 1995 and with those described by Japanese METI (Ministry of Economy, Trade and Industry) of 13 July 1974 and subsequent revisions.

The Sponsor has required the testing activity on this substance to develop notification/submission to regulatory authorities and produce a safety assessment for production and uses.

Procedures and facilities will comply with the requirements of Commission Directive 86/609/EEC concerning the protection of animals used for experimental and other scientific purposes. National legislation, harmonising with this Directive, is defined in Decreto Legislativo No. 116 of 27 January 1992. Aspects of the protocol concerning animal welfare have been approved by the Company's Ethical Committee.

2. TEST ITEM

2.1 Characterisation

It will be the responsibility of the Sponsor to determine, for each batch of test item, the identity, strength, purity and composition, or other characteristics which appropriately define the test item, before its use in the study. The determination of the stability of the test item will also be the Sponsor's responsibility.
A certificate of analysis for the test item should also be supplied.

2.2 Identity

The test item will be [redacted]

The following information refers to the original batch of test item received for the study:

Batch Number : 90409-86-I
Date of expiry : 01 January 2015
Appearance : [redacted]
Storage conditions : Ambient

Should further batches be required to complete the study, full details of batch usage will be maintained in the formulation records but protocol amendments will not be issued.
The amount of the test item received and used at [redacted] will be recorded according to [redacted] standard procedures.

2.3 Safety precautions

The precautions necessary when handling either the test item or prepared formulations of the test item are based on information supplied by the Sponsor. The minimum safety precautions necessary are detailed under the [redacted] Hazard Classification System, according to [redacted] standard procedures.

2.4 Vehicle

The vehicle will be [redacted]

2.5 Formulation procedure

The required amount of [redacted] will be dissolved in the vehicle. The formulations will be prepared daily (concentrations of 0.03, 0.08 and 0.20 mg/ml). Concentrations will be calculated and expressed in terms of test item as supplied.

2.6 Formulation analysis

Analysis will be performed to confirm that the proposed formulation procedure is acceptable and the stability of formulation is satisfactory.
Samples of the formulations prepared in weeks 1 and 4 of the study will also be analysed to check the concentration. Chemical analysis will be carried out by the Analytical Chemistry Department at [redacted] additional cost).

2.7 Disposal

Approximately 1 year after the final report has been issued, remaining amounts of the test item, with the exception of the reserve samples taken for archival purposes, will be returned to the Sponsor.

3. TEST SYSTEM

3.1 Animal supply and acclimatisation

A total of 90 Hsd Sprague Dawley rats (45 males and 45 females), 27-29 days old and within a weight range of approximately 75-99 g, will be obtained from [redacted]

After arrival the weight range for each sex will be determined and the animals will be temporarily identified within the cage by means of a coloured mark on the tail. A health check will then be performed by a veterinarian.

An acclimatisation period of approximately 2 weeks will be allowed before the start of treatment, during which time the health status of the rats will be assessed by thorough observations. Rats considered unsatisfactory will be killed and where appropriate subjected to pathological examination. Unsatisfactory batches of animals will be rejected before the start of treatment.

3.2 Animal husbandry

The animals will be housed in a limited access rodent facility. Animal room controls will be set to maintain temperature and relative humidity at 22°C ± 2°C and 55% ± 15% respectively; actual conditions will be monitored, recorded and the records retained. There will be approximately 15 to 20 air changes per hour and the rooms will be lit by artificial light for 12 hours each day.

The animals will be housed up to 5 of one sex to a cage, in clear polycarbonate cages measuring 59x38.5x20 cm with a stainless steel mesh lid and floor ([redacted]). Each cage tray will hold absorbent paper which will be inspected and changed at least 3 times a week.

Drinking water will be supplied *ad libitum* to each cage via water bottles, except as noted in section 4.3.

A commercially available laboratory rodent diet [redacted] will be offered *ad libitum* throughout the study, except as noted in section 4.3.

There is no information available to indicate that any non-nutrient substance likely to influence the effect of the test item is present in the drinking water or the diet. Records of analyses of water and diet are kept on file at [redacted]

Dated and signed records of activities relating to the day to day running and maintenance of the study in the animal house will be recorded in a Study Day Book.

3.3 Allocation to groups

On the day of allocation (about 7 days prior to the start of treatment) all animals will be weighed. Animals at the extremes of the weight distribution and/or any animal showing signs of ill health will be excluded to leave the required number of animals. The rats will be allocated to the 5 groups by computerised stratified randomisation to give approximately equal initial group mean body weights.
Individuals will be uniquely identified within the study by sex, tattoo on the hind feet, and ear notch and housed up to 5 of one sex per cage.
The cages will be identified by a label and recording the study number, animal numbers and details of treatment.
The arrangement of cages in batteries will be such that cages from each main group will be evenly distributed across the battery (Annex 2) to minimise possible environmental effects.
Any animal showing signs of ill health during the period between allocation and the start of treatment will be subjected to pathological examination as considered appropriate, and replaced with a surplus animal selected from the same batch.

4. EXPERIMENTAL PROCEDURE

4.1 Treatment

4.1.1 Selection of dose levels

Dose levels have been selected in consultation with the Sponsor based on information from preliminary studies.

4.1.2 Dose levels, group size and identification

Each main group will comprise 5 male and 5 female rats. Control and high dose groups will include 5 additional animals per sex to be sacrificed after 2 weeks of recovery. One satellite group for toxicokinetics will comprise 9 male and 9 female animals. The group identification and animal numbers assigned to the treatment are summarised below:

MAIN GROUPS

Group Number:	Treatment (mg/kg/day)+	Level	Main phase		Rat numbers Recovery phase	
			M (even)	F (odd)	M (even)	F (odd)
1	0.0	Control	2 - 10	1 - 9	12 - 20	11 - 19
2	0.3	Low	22 - 30	21 - 29		
3	0.8	Medium	32 - 40	31 - 39		
4	2.0	High	42 - 50	41 - 49	52 - 60	51 - 59

+: in terms of test item as supplied

SATELLITE GROUP

Group Number:	Treatment (mg/kg)+	Level	Rat numbers Males (even)	Females (odd)
5	2.0	High	62 - 78	61 - 77
+: in terms of test item as supplied				

The rat numbers listed above will form the last digits of a computer generated 8 figure animal number (the remaining digits of the animal number will be different for each concurrent study and will serve to ensure unique animal numbering for any study employing computerised data collection). The computerised system used in this study will be the Xybion Path/Tox System, version 4.2.2.

4.1.3 Administration of test item

The test item will be administered orally, by gavage, at a dose volume of 10 ml/kg body weight. Control animals will receive the vehicle alone at the same dose volume.
The dose will be administered to each animal on the basis of the most recently recorded body weight and the volume administered will be recorded for each animal.

4.1.4 Duration of treatment

All main group animals will be dosed once a day, 7 days a week, for a minimum of 4 consecutive weeks followed by a recovery period of 2 weeks for 5 males and 5 females from groups 1 and 4. Satellite group animals will be dosed once only.
All animals from the main groups will be dosed up until the day before necropsy.
No treatment will be given during the recovery period.

4.2 *In vivo* observations

Full records will be maintained for all measurements and observations.

4.2.1 Mortality

Throughout the study, all animals will be checked early in each working day early in the morning and in the afternoon. At weekends and Public Holidays a similar procedure will be followed except that the final check will be carried out at approximately mid-day. This will allow *post mortem* examinations to be carried out during the working period of that day.
Severely debilitated animals will be observed carefully. Animals judged to be *in-extremis* will be killed. A complete necropsy will be performed in all cases as detailed in section 5.4.2 below.

4.2.2 Pre- and post-dose observations (Main groups)

All observations will be recorded for individual animals.
Examination of individual animals for signs of reaction to treatment will be carried out daily prior to dosing and at suitable intervals after dosing. The number and timing of these daily observations will be reviewed by the Study Director at the end of the first week of treatment and, if appropriate, at subsequent intervals.

The number of observations may be reduced, but all animals will be observed at least three times daily during treatment. If more than three daily observations are required after the first week of treatment, an additional cost may be incurred.

4.2.3 Clinical signs and neurotoxicity assessment (Main groups)

Once before commencement of treatment and at least once per week from the start of treatment, each animal will be given a detailed clinical examination. Each animal will be observed in an open arena. The test will include observation of changes in gait and posture, reactivity to handling, presence of clonic or tonic movements, stereotypies or bizarre behaviour and effects on the autonomic nervous system (e.g. lachrymation, piloerection, unusual respiratory pattern).

Once during week 4 of treatment and once during week 2 of recovery an evaluation of sensory reactivity to stimuli of different modalities (e.g. auditory, visual and proprioceptive stimuli) and an assessment of grip strength will also be performed.

4.2.4 Motor activity assessment (MA) (Main groups)

The motor activity (MA) of all animals will be measured once during week 4 of treatment and once during week 2 of recovery by an automated activity recording. Measurements will be performed using a computer generated random order.

4.2.5 Body weight

Each animal will be weighed on the day of allocation to treatment groups, on the day that treatment commences, weekly thereafter and just prior to necropsy. Satellite group animals will be weighed only on the day of dosing.

4.2.6 Food consumption (Main groups)

The weight of food consumed by each cage of rats will be recorded at weekly intervals following allocation. The group mean daily intake per rat will be calculated.

4.3 Clinical pathology investigations (Main groups)

At the end of the 4-week treatment period, individual overnight urine samples will be collected from all surviving animals of the main phase groups under conditions of food and water deprivation. Before starting urine collection, water bottles will be removed from each cage and each animal will receive approximately 10 ml/kg of drinking water by gavage, in order to obtain urine samples suitable for analysis.
On the same day, samples of blood will be withdrawn, prior to necropsy, under isofluorane anaesthesia from the abdominal vena cava from the same animals in the same conditions.
During week 2 of the recovery period, blood and urine samples may also be taken (after consultation with the Sponsor) from all surviving animals under identical conditions in order to re-evaluate any parameters which showed treatment-related changes at measurements performed during the treatment period (additional cost).
Blood samples will be collected and analysed in the same order, a computer-generated random cage order being used.

The blood samples collected will be divided into tubes as follows:

EDTA anticoagulant	for haematological investigations
Heparin anticoagulant	for biochemical tests
Citrate anticoagulant	for coagulation tests

The measurements to be performed on blood and urine samples are listed below:

4.3.1 Haematology

Haematocrit
Haemoglobin
Red blood cell count
Reticulocyte count (if there are signs of anaemia)
Mean red blood cell volume
Mean corpuscular haemoglobin
Mean corpuscular haemoglobin concentration
White blood cell count
Differential leucocyte count
- Neutrophils
- Lymphocytes
- Eosinophils
- Basophils
- Monocytes
- Large unstained cells

Abnormalities of the blood film
Platelets
Prothrombin time

4.3.2 Clinical chemistry

Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Gamma -glutamyltransferase
Urea
Creatinine
Glucose
Triglycerides
Phosphorus
Total bilirubin
Total cholesterol
Total protein
Albumin
Globulin
A/G Ratio
Sodium
Potassium
Calcium
Chloride

4.3.3 Urinalysis

Appearance
Volume
Specific gravity
PH
Protein
Total reducing substances
Glucose
Ketones
Bilirubin
Urobilinogen
Blood

The sediment, obtained from centrifugation at approximately 3000 rpm for 10 minutes, will be examined microscopically for:

Epithelial cells
Poly morphonuclear leucocytes
Erythrocytes
Crystals
Spermatozoa and precursors
Other abnormal components

4.4 Toxicokinetics (Satellite group)

Blood samples will be collected at 9 points from the day of dosing, from all animals of the satellite group as indicated in following scheme:

Group Number:	Treatment (mg/kg)	Animal Number		Time points (hours)
		(Males)	(Females)	
5	2.0	62, 64, 66 68, 70, 72 74, 76, 78	61 ,63, 65 67, 69, 71 73, 75, 77	0, 4, 24 2, 8, 168 6, 48, 216

At each sampling time approximately 0.8 ml blood samples will be collected from the tail vein of each animal as indicated above. Samples will be transferred into tubes containing heparin anticoagulant, centrifuged and the plasma frozen at –20°C. Analysis of the samples will be carried out by the Analytical Chemistry Department of [redacted]
Satellite group animals will be dosed once only and no necropsy will be performed on animals dying during the study or sacrificed at the end of the study. Surviving satellite group animals will be killed at the end of the last bleeding procedure. No necropsy examination will be performed in these animals.

4.5 Terminal studies

4.5.1 Euthanasia

Animals *in extremis* or killed for humane reasons and those that have completed the scheduled test period will be killed with carbon dioxide. All animals of the main groups, including those found dead, will be subjected to necropsy, supervised by a pathologist, as detailed below.

4.5.2 Necropsy (Main groups)

The clinical history of the animal will be studied and a detailed *post mortem* examination will be conducted (including examination of the external surface and orifices).
Changes will be noted, the requisite organs weighed and the required tissue samples preserved in fixative and processed for histopathological examination (see sections 4.5.3 to 4.5.5).

4.5.3 Organ weights (Main groups)

From all animals completing the scheduled test period, the organs indicated in Annex 1 will be dissected free of fat and weighed.
The ratios of organ weight to body weight will be calculated for each animal.
At the discretion of the pathologist, organs may be weighed from animals dying or killed prior to terminal kill.

4.5.4 Tissues fixed and preserved (Main groups)

Samples of all the tissues listed in Annex 1 will be fixed and preserved in 10% buffered formol saline (except eyes which will be fixed in Davidson's fluid; and testes and epididymides which will be fixed in Bouin's solution and all preserved in 70% ethyl alcohol).

4.5.5 Histopathological examination

The tissues required for histopathological examination are listed in Annex 1. After dehydration and embedding in paraffin wax, sections of the tissues will be cut at 5 micrometre thickness and stained with haematoxylin and eosin.
If considered necessary, histological processing may be subcontracted to a GLP certified test site. In such cases, a protocol amendment will be issued, the Sponsor will be informed of the location of the test site and the complete address and name of the Principal Investigator will be presented in the final report.

In the first instance the examination will be restricted as detailed below:

a) Tissues specified in Annex 1 from all animals in the control and high dose group killed after 4 weeks of treatment.
b) Tissues specified in Annex 1 from all animals killed or dying during the treatment period.
c) All abnormalities in all main groups.

The examination could then be extended to include, from all other animals killed after 4 weeks of treatment or 2 weeks of recovery those tissues in which there is any suspicion of treatment-related change at the high dose level.
All histopathological activities which cannot be foreseen before the start of the study (i.e. processing of all abnormalities, tissues of unscheduled deaths in the low, medium dose and recovery groups, target tissues in the low and medium dose) will incur an additional cost.

4.5.6 Photomicrographs

Representative photomicrographs may be taken of any treatment-related lesions. Other photomicrographs may be taken as required by the Sponsor.

5. ANALYSIS OF DATA

5.1 Presentation of data

The data will be summarised and presented in the form of tables or figures. Individual observations and findings for each animal will also be tabulated.

5.2 Statistics

For continuous variables the significance of the differences amongst group means will be assessed by Dunnett's test or a modified *t* test, depending on the homogeneity of data.

6. AMENDMENTS TO THE PROTOCOL

It is not intended to make any amendment to this protocol without authorisation by the Sponsor. However, in the event of difficulty in contacting the Sponsor and/or for humane reasons and/or for the protection of scientific integrity, the testing laboratory retain the right to take independent action.

7. REPORTING

7.1 Interim report

Any unexpected findings during the course of the study will be reported to the Sponsor's Monitoring Scientist immediately.

7.2 Final report

A draft report will be sent to the Sponsor. With the exception of the dated signature of scientists and other professional personnel, the draft report will contain all information and data included in the final report.
Comments made by the Sponsor may be incorporated into the draft, after which it will be issued as the final report.
The final report will include the information and data required by current internationally recognised regulations. One original unbound, one copy bound and a PDF version will be supplied.

March 2005

[redacted]

[redacted]

7.3 Corrections or additions to the final report

Corrections or additions to the approved (i.e. signed) version of the final report will be in the form of an amendment by the Study Director.

8. RECORDS AND ARCHIVES

Full records will be maintained of all aspects of study conduct, together with results of all measurements and observations.
[redacted] will retain all relevant computer stored data generated by electronic on-line capture in a manner fully compliant with Good Laboratory Practice. At the end of the specified period, these data may be despatched to the Sponsor in the original format. If requested, reformatting of these data on alternative media may be carried out and will incur an additional cost.
Prior to commencement of treatment and at each batch change a reserve sample of the test item will be taken and kept under the storage conditions of the bulk supply at [redacted].
The reserve sample(s) of the test item will be retained within the [redacted] archives for a period of 10 years and then destroyed.
If relevant, biological samples obtained for analytical chemistry measurements or similar will be destroyed shortly after the issue of the Final Report, unless otherwise requested by the Sponsor.

All specimens other than the samples described above, raw data, records and documentation generated during the course of this study will be retained at [redacted]. Archiving will be provided for a period of 3 years after which the Sponsor will be contacted for instructions regarding despatch or disposal of the material. As a further option, archiving space can be rented for an additional time.
The signed Final Protocol and the top copy of the Final Report will be despatched to an archive by the Sponsor.

9. QUALITY ASSURANCE

The phases of the study carried out at [redacted] will be subjected to the following quality assurance procedures:

- the protocol will be inspected.
- all procedures relevant to the study will be inspected at intervals adequate to assure the integrity of the study.
- the report will be reviewed to assure that it accurately describes the methods and Standard Operating Procedures and that the results accurately reflect the raw data.

Periodic reports on these activities will be made to management and the Study Director.
All raw data pertaining to the study will be available for inspection by the Sponsor's representative and regulatory authorities (following authorisation from the Sponsor).

10. LOCATION OF THE STUDY

[redacted]

11. PROJECTED TIME PLAN

		Date
1.	Start of treatment	: End of March 2005
2.	End of *in vivo* phase	: Mid May 2005
3.	End of histopathological examination	: First half of June 2005
4.	QAU audited draft report to Sponsor	: 3.5 months after the first day of treatment

ANNEX 1. TISSUE PROCESSING

Organs / Tissues	Weight	Fixation Preservation	Microscopic Examination
Abnormalities		✓	✓
Adrenal glands	✓	✓	✓
Bone marrow (from sternum)		✓	✓
Brain	✓	✓	✓
Caecum		✓	✓
Colon		✓	✓
Duodenum		✓	✓
Epididymides	✓	✓	✓
Eyes		✓	*
Heart	✓	✓	✓
Ileum (including Peyer's patches)		✓	✓
Jejunum		✓	✓
Kidneys	✓	✓	✓
Liver	✓	✓	✓
Lungs (including mainstem bronchi)		✓	✓
Lymph nodes - cervical		✓	✓
Lymph nodes - mesenteric		✓	✓
Ovaries	✓	✓	✓
Oviducts[a]		✓	✓
Parathyroid glands[b]		✓	✓
Pituitary gland		✓	✓
Prostate gland		✓	✓
Rectum		✓	✓
Sciatic nerve		✓	✓
Seminal vesicles		✓	*
Spinal column		✓	✓
Spinal cord		✓	✓
Spleen	✓	✓	✓
Stomach		✓	✓
Testes	✓	✓	✓
Thymus (where present)	✓	✓	✓
Thyroid	✓	✓	✓
Trachea		✓	✓
Urinary bladder		✓	✓
Uterus - cervix		✓	✓

*: to be examined if indicated by signs of toxicity or target organ involvement.

a: weighed and preserved with ovaries

b: weighed and preserved with thyroid gland

ANNEX 2. GROUP AND CAGE ARRANGEMENT ON BATTERY

MAIN PHASE

Group Number:	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
1	0.0	Control	2 - 10	1 - 9	1	7
2	0.3	Low	22 - 30	21 - 29	3	9
3	0.8	Medium	32 - 40	31 - 39	4	10
4	2.0	High	42 - 50	41 - 49	5	11

+: in terms of test item as supplied

RECOVERY PHASE

Group Number:	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
1	0.0	Control	12 - 20	11 - 19	2	8
4	2.0	High	52 - 60	51 - 59	6	12

+: in terms of test item as supplied
°: No treatment will be given during the recovery period.

SATELLITE GROUP

Group Number:	Treatment (mg/kg/day)+	Level	Rat numbers		Cage numbers	
			M (even)	F (odd)	M	F
5	2.0	High	62 - 78	61 - 77	13-15	17-19

+: in terms of test item as supplied

Group/Sex
Cage no.

#

= To be inserted in the final report

PROTOCOL APPROVAL PAGE

STUDY TITLE : 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

TEST FACILITY : [redacted]

RTC ENQUIRY NO. : [redacted]

TEST ITEM : [redacted]

APPROVED BY : [redacted] 15-Mar-2005
Study Director Date

APPROVED BY : [redacted] 15-Mar-2005
Responsible for Animal Welfare Date

RELEASED BY : [redacted] 15 Mar 2005
Scientific Director Date

SPONSOR : [redacted]

AUTHORISED BY SPONSOR* : [redacted] 18/03/2005
Date

Name and Title : [redacted], Industrial Toxicology

* Please print or type your name and company status below your signature.

Haematology

A decrease in white blood cell was observed in the high dose animals (approximately 19%) and in the mid-dose females (approximately 17%) at the end of the treatment period. This reduction was still evident at the end of the recovery period (11% and 16% in females and males respectively). The decrement comprised both the lymphocytes and the neutrophils in the males, which had 29%, 19% and 39% less neutrophils at the high, medium and low dose, respectively. Such an evident decrement was not observed in the females.

In addition, the prothrombin time was slightly increased in high dose males (14%). This could reflect the alteration in hepatic functions as indicated by the clinical chemistry results.
This change showed a trend for recovery at the end of treatment-free period, when an increase of 8% was observed.

The other differences observed in the haematological parameters (RBC, HGB, HCT, MCHC) were considered to be incidental and of no toxicological significance, since they were observed only during the recovery phase and no other alterations in the same haematological parameters were observed during the treatment period.

Clinical Chemistry

The statistically significant changes in clinical chemistry parameters are summarized below:

Parameters	2M	3M	4M	4M Rec	2F	3F	4F	4F Rec
AP		+18%	+33%	+41%				
ALT		+309%	+219%					-29%
AST		+58%	+61%			-60%	-33%	-37%
BILT			+70%					
CHOL	-34%	-23%		+76%			+20%	+31%
GLU								-27%
TRI		-51%		-45%			+24%	
Urea			+48%	+35%			-15%	-35%
Crea				-34%				
Prot	-9%		-16%	-11%				+9%
Alb			-13%					
Glo	-14%	-11%	-23%	-26%			+17%	+20%
A/G Ratio							+2%	-1%
Cl			+2%				-9%	-7%
Phos		-9%	-21%					-2%
Na		+4%		-2%				+12%
K								

Changes observed at the clinical chemistry investigations performed during week 4 of treatment revealed alteration of liver function in the high dose males and, to a lesser extent, in two mid-dose males (increases in hepatic markers alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and total bilirubin, decrements of protein, globulin and albumin). These changes were generally dose related (from approximately 20% to approximately 3 fold) and in some high dose animals values were outside the range of historical data.

The above mentioned changes could reflect an alteration in the hepatic function.
A reversibility of these changes was observed for the aminotransferase enzymes at the clinical pathology performed during week 2 of recovery.
No significant hepatic marker alterations were observed in females.

Urea plasma levels were increased in high dose animals, while creatinine and inorganic phosphorus showed a decrement in the same group. At the end of the recovery period, no complete reversibility of such changes was observed. The cause of these changes however remains unclear and could not be conclusively attributed to the test item.
In addition, changes of chloride and sodium serum levels were insufficient in magnitude to be of biological significance.

The other alterations observed during the recovery period in both sexes were considered to be incidental and of no toxicological significance.

Urinalysis

No alterations in urine were observed which could be attributed to treatment.

[redacted]
Study Clinical Pathologist

date: 19 December 2005

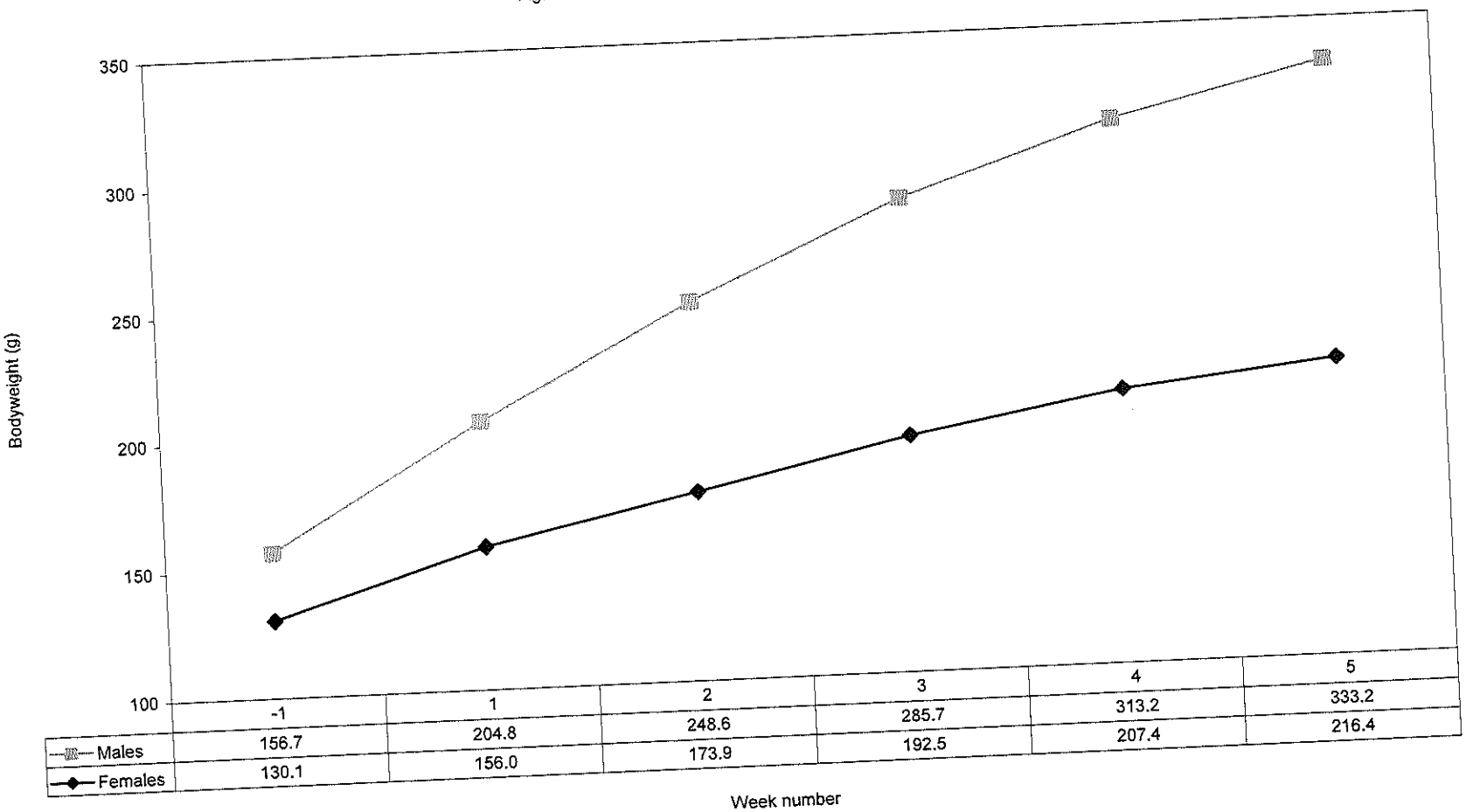
[redacted]

[redacted] 4-WEEK ORAL TOXICITY STUDY IN RATS FOLLOWED BY A 2 WEEK RECOVERY PERIOD

ADDENDUM VIII - Historical control data

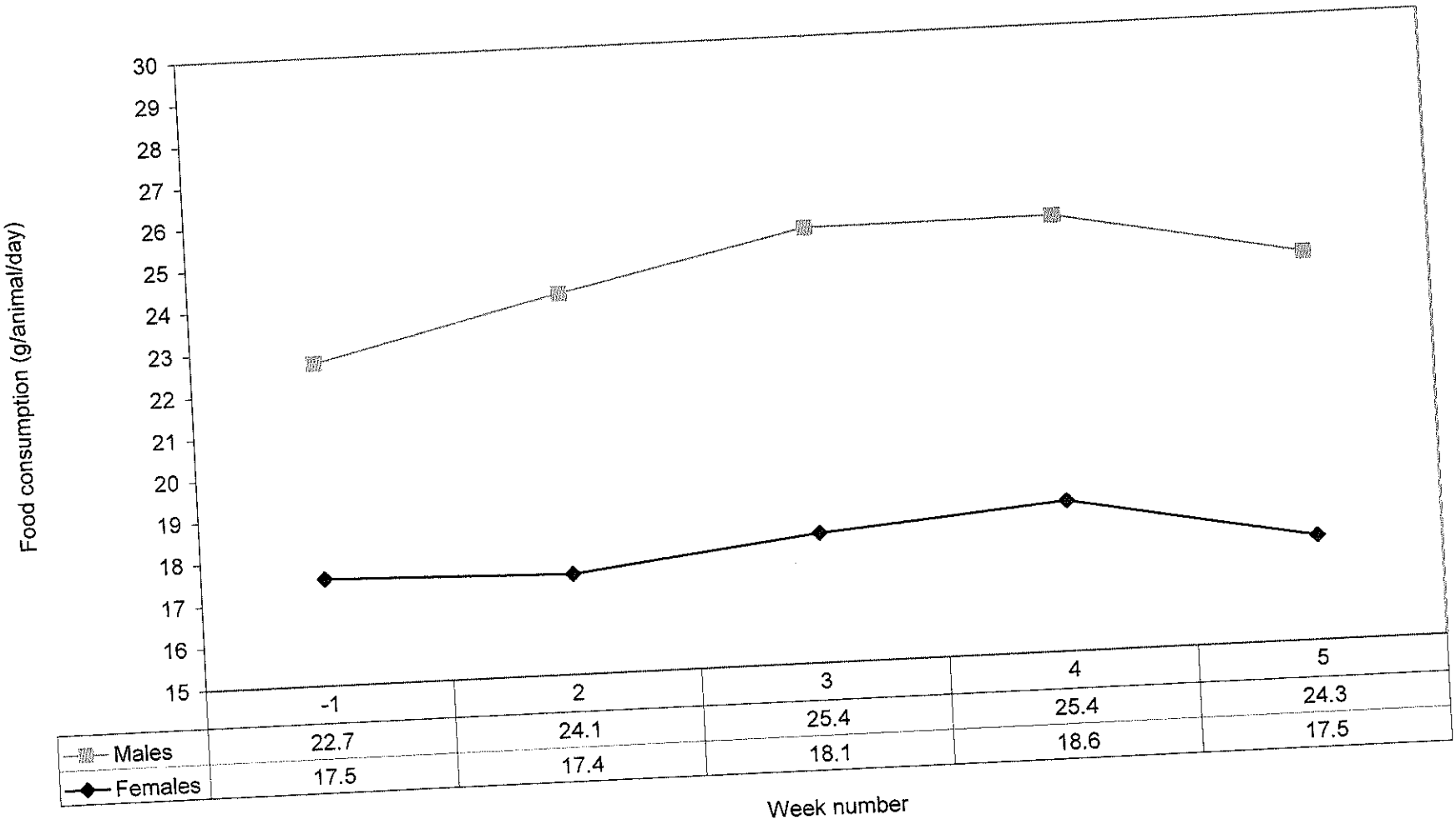
STUDY NO.: [redacted]

Fig. 1: 4 week Studies - Bodyweight - Both sexes



	-1	1	2	3	4	5
Males	156.7	204.8	248.6	285.7	313.2	333.2
Females	130.1	156.0	173.9	192.5	207.4	216.4

Fig. 2: 4 week Studies - Food consumption - Both sexes



	-1	2	3	4	5
Males	22.7	24.1	25.4	25.4	24.3
Females	17.5	17.4	18.1	18.6	17.5

Fig. 3: 4 week Studies - Haematology - Males

Parameter	Units	No.	Maximum	Minimum	Mean	Std Dev
Haemoglobin	g/dl	152	17.9	13.4	**16.1**	0.7
Red Blood Cell Count	10^12/l	152	9.1	7.1	**8.4**	0.4
Haematocrit	%	152	53.2	39.0	**47.8**	2.4
Mean Corpuscular Hb	pg	152	20.4	17.8	**19.0**	0.5
Mean Corpusc. Hb conc.	g/dl	152	36.5	31.4	**33.6**	1.1
Mean Red Blood Cell Vol.	fl	152	61.1	51.1	**56.7**	1.8
White Blood Cell Count	10^9/l	152	21.5	8.1	**12.9**	2.4
Neutrophils	%	152	57.0	5.2	**11.3**	5.3
Lymphocytes	%	152	91.9	37.4	**83.1**	5.4
Monocytes	%	152	5.7	1.1	**2.5**	0.8
Eosinophils	%	152	6.8	0.3	**1.3**	0.7
Basophils	%	152	0.6	0.1	**0.3**	0.1
Large Unstained Cells	%	152	2.8	0.5	**1.4**	0.4
Platelets	10^9/l	151	1413.0	370.0	**1028.8**	153.0
Prothrombin Time	sec.	75	18.2	10.4	**13.0**	1.3

Fig. 4: 4 week Studies - Haematology - Females

Parameter	Units	No.	Maximum	Minimum	Mean	Std Dev
Haemoglobin	g/dl	161	16.8	11.5	**15.3**	0.7
Red Blood Cell Count	10^12/l	161	8.9	6.4	**8.0**	0.4
Haematocrit	%	161	49.6	33.9	**44.4**	2.4
Mean Corpuscular Hb	pg	161	20.9	17.6	**19.1**	0.6
Mean Corpusc. Hb conc.	g/dl	161	37.7	31.2	**34.5**	1.4
Mean Red Blood Cell Vol.	fl	161	60.2	51.5	**55.4**	1.8
White Blood Cell Count	10^9/l	161	15.4	3.7	**8.8**	2.2
Neutrophils	%	161	27.1	5.0	**10.9**	4.3
Lymphocytes	%	161	91.3	66.8	**83.7**	4.6
Monocytes	%	161	4.4	0.7	**2.3**	0.8
Eosinophils	%	161	4.6	0.5	**1.7**	0.6
Basophils	%	161	0.5	0.0	**0.2**	0.1
Large Unstained Cells	%	161	2.2	0.5	**1.2**	0.4
Platelets	10^9/l	161	1427.0	458.0	**1065.7**	141.5
Prothrombin Time	sec.	77	15.4	11.2	**13.1**	1.0

Fig. 5: 4 week Studies - Serum Chemistry - Males

Parameter	Units	No.	Maximum	Minimum	Mean	Std Dev
Albumin/Globulin ratio		37	1.1	0.5	**1.0**	0.1
Albumin	g/dl	82	4.4	2.4	**3.5**	0.4
Alanine Amino-Transferase	U/l	162	78.0	19.1	**44.8**	11.4
Alkaline Phosphatase	U/l	162	769.7	162.3	**340.6**	113.5
Aspartate Amino-Transferase	U/l	162	215.3	38.4	**92.6**	31.3
Total Bilirubin	mg/dl	162	0.3	0.0	**0.1**	0.0
Calcium	mmol/l	162	3.0	2.3	**2.6**	0.1
Total Cholesterol	mg/dl	162	561.6	67.3	**105.2**	40.1
Chloride	mmol/l	162	106.6	87.7	**96.3**	3.9
Creatinine	mg/dl	162	0.8	0.3	**0.5**	0.1
Gamma-Glutamyl Transferase	U/l	22	3.2	0.0	**1.2**	0.9
Globulin	g/dl	37	4.7	2.9	**3.5**	0.3
Glucose	mg/dl	162	166.3	59.8	**113.2**	21.3
Potassium	mmol/l	162	5.8	2.8	**3.9**	0.5
Sodium	mmol/l	161	170.4	132.1	**146.6**	9.0
Inorganic Phosphorus	mg%P	22	8.8	6.5	**7.8**	0.7
Total Protein	g/dl	162	7.5	5.8	**6.8**	0.4
Triglycerides	mg/dl	15	56.6	25.7	**42.2**	10.4
Urea	mg/dl	162	88.1	18.5	**41.1**	10.3

Fig. 6: 4 week Studies - Serum Chemistry - Females

Parameter	Units	No.	Maximum	Minimum	Mean	Std Dev
Albumin/Globulin ratio		37	1.2	1.0	**1.1**	0.1
Albumin	g/dl	82	4.7	3.2	**3.8**	0.4
Alanine Amino-Transferase	U/l	162	52.5	13.5	**34.1**	8.7
Alkaline Phosphatase	U/l	162	769.8	90.5	**248.4**	99.5
Aspartate Amino-Transferase	U/l	162	144.7	29.5	**78.2**	20.2
Total Bilirubin	mg/dl	162	0.2	0.0	**0.1**	0.0
Calcium	mmol/l	162	2.8	2.3	**2.6**	0.1
Total Cholesterol	mg/dl	162	363.6	49.2	**98.5**	29.4
Chloride	mmol/l	162	105.5	81.5	**97.5**	4.5
Creatinine	mg/dl	162	0.8	0.3	**0.6**	0.1
Gamma-Glutamyl Transferase	U/l	22	1.2	0.1	**0.6**	0.3
Globulin	g/dl	37	3.6	3.0	**3.3**	0.2
Glucose	mg/dl	162	219.8	35.1	**109.3**	21.8
Potassium	mmol/l	162	4.8	2.8	**3.6**	0.4
Sodium	mmol/l	162	168.3	132.4	**145.9**	8.6
Inorganic Phosphorus	mg%P	22	8.3	6.7	**7.5**	0.5
Total Protein	g/dl	162	7.8	5.7	**6.8**	0.4
Triglycerides	mg/dl	15	65.1	20.0	**36.6**	15.5
Urea	mg/dl	162	85.5	19.3	**47.4**	10.2

Fig. 7: 4 week Studies - Urinalysis - Males

Parameter	Units	No.	Maximum	Minimum	Mean	Std Dev
Specific Gravity		108	1.06	1.01	**1.03**	0.01
Urine Volume	ml	128	12.50	1.50	**4.91**	2.05

Fig. 8: 4 week Studies - Urinalysis - Females

Parameter	Units	No.	Maximum	Minimum	Mean	Std Dev
Specific Gravity		107	1.05	1.01	**1.03**	0.01
Urine Volume	ml	95	13.00	1.00	**4.49**	2.61

Fig. 9: 4 week Studies - Terminal Bodyweight - Males

TBW	No.	Maximum	Minimum	Mean	Std Dev
TBW	151	398.8	274.1	**332.8**	26.1

Fig. 10: 4 week Studies - Terminal Bodyweight - Females

TBW	No.	Maximum	Minimum	Mean	Std Dev
TBW	152	263.8	182.3	**217.0**	15.2

Fig. 11: 4 week Studies - Relative Organ Weights - Males (% of bodyweight)

Organ	No.	Maximum	Minimum	Mean	Std Dev
Adrenals	162	0.024	0.011	**0.016**	0.002
Brain	161	0.750	0.447	**0.530**	0.042
Epididymides	75	0.438	0.252	**0.313**	0.034
Heart	162	0.453	0.339	**0.387**	0.023
Kidneys	162	1.492	0.660	**0.792**	0.077
Liver	162	7.544	3.320	**4.523**	0.542
Pituitary	107	0.004	0.002	**0.003**	0.000
Spleen	162	0.368	0.157	**0.252**	0.029
Testes	162	1.448	0.912	**1.110**	0.082
Thymus	65	0.222	0.071	**0.148**	0.032
Thyroid	107	0.011	0.004	**0.007**	0.001

Fig. 12: 4 week Studies - Relative Organ Weights - Females (% of bodyweight)

Organ	No.	Maximum	Minimum	Mean	Std Dev
Adrenals	161	0.039	0.021	**0.029**	0.003
Brain	161	0.879	0.638	**0.747**	0.050
Heart	161	0.478	0.361	**0.412**	0.024
Kidneys	161	1.290	0.592	**0.766**	0.070
Liver	161	7.220	3.350	**4.100**	0.416
Ovaries	151	0.055	0.019	**0.038**	0.006
Pituitary	106	0.008	0.003	**0.005**	0.001
Spleen	161	0.427	0.254	**0.322**	0.034
Thymus	64	0.221	0.087	**0.152**	0.027
Thyroid	106	0.015	0.003	**0.009**	0.002
Uterus	116	0.569	0.108	**0.194**	0.065

Fig. 13: 4 week Studies - Microscopic Pathology - Males

Organs/Tissues	Number Examined	Diagnoses	Incidence Observed	%
Cervical nodes	136	REACTIVE HYPERPLASIA	17	12.50%
Colon	137	DISTENSION	7	5.11%
Duodenum	137	VILLOUS NECROSIS	1	0.73%
Eyes	87	ACUTE INFLAMMATION	1	1.15%
	87	HAEMORRHAGE	1	1.15%
Harderian glands	87	CHRONIC INFLAMMATION	22	25.29%
	87	PORPHYRIN ACCUMULATION	1	1.15%
Heart	157	CHRONIC INFLAMMATION	30	19.11%
Ileum	137	DISTENSION	1	0.73%
Kidneys	157	CHRONIC INFLAMMATION	9	5.73%
	157	CHRONIC PROGRESSIVE NEPHROSIS	12	7.64%
	157	CORTICAL TUBULAR CELL BASOPHILIA	44	28.02%
	157	CORTICAL TUBULAR DILATATION	37	23.57%
	157	HYALINE CASTS	5	3.18%
	157	HYDRONEPHROSIS	1	0.64%
Liver	157	BILE DUCT PROLIFERATION	2	1.27%
	157	CENTRILOBULAR HEPATOCYTIC VACUOLATION	2	1.27%
	157	CHRONIC INFLAMMATION	65	41.40%
	157	CLEAR CELL CHANGE	13	8.28%
Lungs	157	AGGREGATIONS OF ALVEOLAR MACROPHAGES	13	8.28%
	157	ALVEOLAR HAEMORRHAGE	21	13.38%
	157	CHRONIC INFLAMMATION	104	66.24%
	157	EOSINOPHIL INFILTRATION	3	1.91%
	157	FRAGMENTS OF BONE	1	0.64%
	157	HAIR EMBOLUS	1	0.64%
	157	OEDEMA	4	2.55%
	157	PERIBRONCHIAL LYMPHOID HYPERPLASIA	21	13.38%
	157	PNEUMONIA	3	1.91%
	157	VASCULAR MINERALIZATION	7	4.46%
Lymph nodes	10	HAEMORRHAGE	2	20.00%
	10	REACTIVE HYPERPLASIA	2	20.00%
Mesenteric nodes	137	REACTIVE HYPERPLASIA	1	0.73%
Pancreas	87	CYSTIC CHANGE	1	1.15%
	87	EOSINOPHIL INFILTRATION	1	1.15%
Pituitary	86	DEVELOPMENTAL CYST/S	1	1.16%

Prostate	147	CHRONIC INFLAMMATION	15	10.20%
	147	OEDEMA	1	0.68%
Rectum	137	DISTENSION	2	1.46%
Seminal vesicles	70	COLLOID DISTENSION	10	14.29%
Stomach	137	CHRONIC INFLAMMATION	2	1.46%
	137	SQUAMOUS METAPLASIA OF MUCOSAL GLANDS	1	0.73%
Testes	157	SEMINIFEROUS TUBULES ATROPHY	1	0.64%
	157	TUBULAR GIANT CELLS	1	0.64%
Thymus	137	HAEMORRHAGE	2	1.46%
Thyroid	137	ECTOPIC THYMIC TISSUE	4	2.92%
Trachea	137	CHRONIC INFLAMMATION	1	0.73%
Urinary bladder	137	DISTENSION	3	2.19%
	137	PROTEINACEOUS PLUG	8	5.84%

Fig. 14: 4 week Studies - Microscopic Pathology - Females

Organs/Tissue	Number Examined	Diagnoses	Incidence Observed	%
Brain	157	HYDROCEPHALUS	1	0.64%
Cervical nodes	136	REACTIVE HYPERPLASIA	11	8.09%
Colon	137	DISTENSION	5	3.65%
	137	LYMPHOID HYPERPLASIA	1	0.73%
Eyes	87	ACUTE INFLAMMATION	1	1.15%
	87	CATARACT	1	1.15%
	87	DETACHMENT OF RETINA	1	1.15%
	87	KERATITIS	2	2.30%
Harderian glands	87	CHRONIC INFLAMMATION	16	18.40%
	87	HAEMORRHAGE	1	1.15%
Heart	157	CHRONIC INFLAMMATION	7	4.46%
Ileum	137	LYMPHOID HYPERPLASIA	2	1.46%
Jejunum	137	LYMPHOID HYPERPLASIA	2	1.46%
Kidneys	157	CHRONIC INFLAMMATION	8	5.10%
	157	CHRONIC PROGRESSIVE NEPHROSIS	1	0.64%
	157	CORTICAL TUBULAR CELL BASOPHILIA	8	5.10%
	157	CORTICAL TUBULAR DILATATION	4	2.54%
	157	CORTICAL CYST	1	0.64%
	157	HYALINE CASTS	1	0.64%
	157	HYDRONEPHROSIS	2	1.27%
	157	MINERALIZATION	36	22.92%
	157	PELVIC EPITHELIAL HYPERPLASIA	3	1.91%
Liver	157	CHRONIC INFLAMMATION	65	41.40%
	157	HAEMORRHAGE	1	0.64%
	157	HEPATOCYTIC NECROSIS	2	1.27%
	157	CLEAR CELL CHANGE	6	3.82%
Lungs	157	AGGREGATIONS OF ALVEOLAR MACROPHAGES	11	7.01%
	157	ALVEOLAR EPITHELIALIZATION	2	1.27%
	157	ALVEOLAR HAEMORRHAGE	14	8.92%
	157	CHRONIC INFLAMMATION	99	63.05%
	157	EMPHYSEMA	1	0.64%
	157	EOSINOPHILIC INFILTRATION	1	0.64%
	157	FRAGMENTS OF BONE	1	0.64%
	157	HAIR EMBOLUS	2	1.27%
	157	OEDEMA	4	2.55%
	157	PERIBRONCHIAL LYMPHOID HYPERPLASIA	21	13.38%
	157	PNEUMONIA	16	10.19%
	157	VASCULAR MINERALIZATION	3	1.91%

Lymph nodes	10	HAEMORRHAGE	1	10.00%
	10	REACTIVE HYPERPLASIA	4	40.00%
Ovaries	157	LUTEIN CYST	2	1.27%
	157	MINERALIZZATION	1	0.64%
Parathyroid glands	71	BRANCHIAL CYST/S	1	1.41%
Pituitary	86	DEVELOPMENTAL CYST/S	3	3.49%
Rectum	137	ACUTE INFLAMMATION	1	0.73%
	137	DISTENSION	2	1.46%
	137	LYMPHOCYTIC INFILTRATION	1	0.73%
	137	LYMPHOID HYPERPLASIA	1	0.73%
Skeletal muscle	87	CHRONIC INFLAMMATION	1	1.15%
Skin	87	KERATIN CYST	1	1.15%
Spinal cord	136	EPIDERMOID INCLUSION CYST/S	1	0.74%
Spleen	157	CONGENITAL ABNORMALITY	1	0.64%
Stomach	137	SQUAMOUS METAPLASIA OF MUCOSAL GLANDS	1	0.73%
	137	ECTOPIC THYROID TISSUE	1	0.73%
	137	HAEMORRHAGE	1	0.73%
Thyroid	137	ECTOPIC THYMIC TISSUE	5	3.65%
Tongue	87	CYST/S	1	1.15%
Urinary bladder	137	EPITHELIAL HYPERPLASIA	1	0.73%
Uterus	137	ENDOMETRIAL CYST	1	0.73%
	137	GLANDULAR DILATATION	1	0.73%
	137	HYDROMETRA	9	6.57%